ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Revlimid 2.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 2.5 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 73.5 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsule.

Blue-green/white capsules, size 4, 14.3 mm, marked “REV 2.5 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma
Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes
Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration
Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < $1.0 \times 10^9/L$, and/or platelet counts are < $50 \times 10^9/L$. 
**Recommended dose**

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10^9/L</td>
<td>Stop lenalidomide dosing for remainder of cycle^a</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10^9/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

^a If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>Neutrophil count</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).
Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10⁹/L, and/or platelet counts are < 75 x 10⁹/L.

**Recommended dose**
The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 1 or 2 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Lenalidomide</th>
<th>Melphalan</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mg*</td>
<td>0.18 mg/kg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>7.5 mg</td>
<td>0.14 mg/kg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>5 mg</td>
<td>0.10 mg/kg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

*If neutropenia is the only toxicity at any dose level, add granulocyte stimulating factor (G-CSF) and maintain the dose level of lenalidomide

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 25 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x 10⁹/L</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10⁹/L*</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level once daily</td>
</tr>
</tbody>
</table>

*If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.

In case of neutropenia, the use of growth factors in patient management should be considered.

**Multiple myeloma with at least one prior therapy**

**Recommended dose**
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of
each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10⁹/L, and/or platelet counts < 75 x 10⁹/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10⁹/L.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level -1</td>
<td>15 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>10 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 30 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

**Myelodysplastic syndromes**

Lenalidomide treatment must not be started if the ANC < 0.5 x 10⁹/L and/or platelet counts < 25 x 10⁹/L.

**Recommended dose**

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reduction steps

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>Dose level -1</th>
<th>Dose level -2</th>
<th>Dose level -3</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg once daily on days 1-21 every 28 days</td>
<td>5.0 mg once daily on days 1-28 every 28 days</td>
<td>2.5 mg once daily on days 1-28 every 28 days</td>
<td>2.5 mg every other day 1-28 every 28 days</td>
</tr>
</tbody>
</table>

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x 10⁹/L - &lt; 50 x 10⁹/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10⁹/L at any time</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

All patients

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

Older people

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).
• Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

No dose adjustment is proposed for patients older than 75 years treated with lenalidomide in combination with melphalan and prednisone.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years (see section 4.4).

• Multiple myeloma with at least one prior therapy

The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

*Patients with renal impairment*

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma or myelodysplastic syndromes. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

• Multiple myeloma

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily(^1)</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily(^2)</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

\(^1\) The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

\(^2\) In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.
• **Myelodysplastic syndromes**

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>Starting dose 5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg once daily (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg once every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
</tbody>
</table>

**Patients with hepatic impairment**
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

**Method of administration**

Oral use.
Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

### 4.4 Special warnings and precautions for use

**Pregnancy warning**
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.
Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*  
- Premature ovarian failure confirmed by a specialist gynaecologist  
- Previous bilateral salpingo-oophorectomy, or hysterectomy  
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling

For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child  
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment  
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception  
- She should be capable of complying with effective contraceptive measures  
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy  
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test  
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation  
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential  
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.  
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding  
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant  
- Levonorgestrel-releasing intrauterine system (IUS)
• Medroxyprogesterone acetate depot
• Tubal sterilisation
• Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
• Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected
teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and
haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6% in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8). Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p-treated patients compared to 0.0% in MPp+p-treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p-treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8, Haemorrhagic disorders).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Myelodysplastic syndromes
Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

**Infection with or without neutropenia**
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

**Renal impairment**
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

**Thyroid disorders**
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

**Peripheral neuropathy**
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

**Tumour lysis syndrome**
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

**Allergic reactions**
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**
SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Lactose intolerance**
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Unused capsules**
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

**Second primary malignancies**
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.
In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

**Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS**

- **Karyotype**
  Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- **TP53 status**
  A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8).

**Hepatic disorders**

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.
Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**
There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min (see section 4.2 and 4.8).

**Cataract**
Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

### 4.5 Interaction with other medicinal products and other forms of interaction
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**
Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**
Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.
There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).

Interactions with P-glycoprotein (P-gp) inhibitors
*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg).

Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.
4.8 Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).
The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 1: Advers reactions reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
<td>Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
<td></td>
</tr>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
<td></td>
</tr>
<tr>
<td>Squamous skin cancer*</td>
<td>Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Neutropenia*, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenias</td>
<td>Neutropenia*, Thrombocytopenia ^, Anaemia, Leucopenias</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia, Pancytopenia</td>
<td>Febrile neutropenia, Pancytopenia</td>
<td></td>
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<tr>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td></td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hypersensitivity^</td>
<td>Hypercoagulation, Coagulopathy</td>
<td></td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
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<td>------------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hypothyroidism</td>
<td>Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td>Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Very Common Depression, Insomnia Uncommon Loss of libido</td>
<td>Common Depression, Insomnia</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired</td>
<td>Common Cerebrovascular accident, Dizziness, Syncope Uncommon Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Very Common Cataracts, Blurred vision Common Reduced visual acuity</td>
<td>Common Cataract Uncommon Blindness</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Common Deafness (Including Hypoacusis), Tinnitus</td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Common Atrial fibrillation, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td>Common Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Hypotension, Hypertension, Ecchymosis^</td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Very Common Dyspnoea, Epistaxis^</td>
<td>Common Respiratory distress, Dyspnoea</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ADRs/Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
<td>Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
<td></td>
</tr>
<tr>
<td>Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding), Dry mouth, Stomatitis, Dysphagia</td>
<td>Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding), Dry mouth, Stomatitis, Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Uncommon Colitis, Caecitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Abnormal liver function tests</td>
<td>Common Cholestasis, Abnormal liver function tests</td>
<td></td>
</tr>
<tr>
<td>Uncommon Hepatic failure^</td>
<td>Uncommon Hepatic failure^</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common Rashes, Pruritus</td>
<td>Common Rashes</td>
<td></td>
</tr>
<tr>
<td>Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon Skin discoloration, Photosensitivity reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia</td>
<td>Common Muscular weakness, Bone pain</td>
<td></td>
</tr>
<tr>
<td>Common Muscular weakness, Joint swelling, Myalgia</td>
<td>Uncommon Muscular weakness, Bone pain</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common Renal failure (including acute)</td>
<td>Uncommon Renal tubular necrosis</td>
<td></td>
</tr>
<tr>
<td>Common Haematuria^, Urinary retention, Urinary incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon Acquired Fanconi syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Erectile dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors)</td>
<td>Common Fatigue, Pyrexia, Asthenia</td>
<td></td>
</tr>
<tr>
<td>Common Chest pain, Lethargy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common C-reactive protein increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Fall, Contusion^</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^See section 4.8 description of selected adverse reactions

* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls
Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

**Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide**

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Pneumonia^, Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia^, Neutropenia^, Leucopenias</td>
<td>Thrombocytopenia^, Neutropenia^, Leucopenias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile Neutropenia^</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Hyperglycaemia^, Decreased appetite</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>Hyperglycaemia^, Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iron overload, Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altered mood^</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dizziness, Headache</td>
<td>Acute myocardial infarction^, Atrial fibrillation^, Cardiac failure^</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypertension, Haematoma</td>
<td>Bronchitis</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Epistaxis^</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Very Common Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation Common Dry mouth, Dyspepsia</td>
<td>Common Diarrhoea, Nausea, Toothache</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Common Abnormal liver function tests</td>
<td>Common Abnormal liver function tests</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Very Common Rashes, Dry Skin, Pruritus</td>
<td>Common Rashes, Pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Very Common Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td>Common Back pain</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)</td>
<td>Common Renal failure</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)</td>
<td>Common Pyrexia</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)</td>
<td>Common Fall</td>
</tr>
</tbody>
</table>

\(^{*}\)See section 4.8 description of selected adverse reactions
\(^{*}\)Adverse events reported as serious in myelodysplastic syndromes clinical trials
\(^{-}\)Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event
\(^{#}\)Algorithm applied for myelodysplastic syndromes:
- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.
Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Rare Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Not Known Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Not Known Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Not Known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^</td>
<td>Not Known Acute hepatic failure^, Hepatitis toxic^</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Uncommon Angioedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^, Not Known Leukocytoclastic vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

^see section 4.8 description of selected adverse reactions

Description of selected adverse reactions

Teratogenicity
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

- Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).
The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**

An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone or as monotherapy in patients with myelodysplastic syndromes treated with lenalidomide monotherapy (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).
Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second primary malignancies
*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Acute myeloid leukaemia

- Multiple myeloma

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- Myelodysplastic syndromes

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

Gastrointestinal disorders
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.
The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS time, months (95% CI)⁷</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI] ; p-value⁶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| PFS² – (months)                     |             |               |              |
| Median PFS time, months (95% CI)⁷   | 42.9 (38.1, 47.4) | 40.0 (36.2, 44.2) | 35.0 (30.4, 37.8) |
| HR [95% CI] ; p-value⁶              |             |               |              |
| Rd vs MPT                           | 0.74 (0.63, 0.86); <0.001 |          |              |
| Rd vs Rd18                          | 0.92 (0.78, 1.08); 0.316 |          |              |
| Rd18 vs MPT                         | 0.80 (0.69, 0.93); 0.004 |          |              |

| Overall survival (months)          |             |               |              |
| Median OS time, months (95% CI)⁷   | 58.9 (56.0, NE) | 56.7 (50.1, NE) | 48.5 (44.2, 52.0) |
| HR [95% CI] ; p-value⁶              |             |               |              |
| Rd vs MPT                           | 0.75 (0.62, 0.90); 0.002 |          |              |
| Rd vs Rd18                          | 0.91 (0.75, 1.09); 0.305 |          |              |
| Rd18 vs MPT                         | 0.83 (0.69, 0.99); 0.034 |          |              |

| Follow-up (months)                 |             |               |              |
| Median (min, max); all patients    | 40.8 (0.0, 65.9) | 40.1 (0.4, 65.7) | 38.7 (0.0, 64.2) |

| Myeloma response n (%)             |             |               |              |
| CR                                  | 81 (15.1)  | 77 (14.2) | 51 (9.3) |
| VGPR                                | 152 (28.4) | 154 (28.5) | 103 (18.8) |
| PR                                  | 169 (31.6) | 166 (30.7) | 187 (34.2) |
| Overall response: CR, VGPR, or PR   | 402 (75.1) | 397 (73.4) | 341 (62.3) |

| Duration of response – (months)⁵   |             |               |              |
| Median (95% CI)⁷                   | 35.0 (27.9, 43.4) | 22.1 (20.3, 24.0) | 22.3 (20.2, 24.9) |

AMT = antimielyoma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≥ 18 cycles; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

³ The median is based on the Kaplan-Meier estimate.
⁴ The 95% CI about the median.
⁵ The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
⁶ The p-value is based on the Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
⁷ The median is the univariate statistic without adjusting for censoring.
⁸ Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category, Data cutoff date = 24 May 2013).
⁹ data cut 24 May 2014

**Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients not eligible for transplant**

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The
study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of three treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5:

<table>
<thead>
<tr>
<th>Table 5: Summary of overall efficacy data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator-assessed PFS – (months)</strong></td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td><strong>PFS2 – (months)</strong></td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td><strong>Overall survival (months)</strong></td>
</tr>
<tr>
<td>Median OS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td>Follow-up (months)</td>
</tr>
<tr>
<td>Median (min, max): all patients</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
</tr>
<tr>
<td>Response Not Evaluable (NE)</td>
</tr>
<tr>
<td>Investigator-assessed Myeloma response n (CR+PR) – (months)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response. * The median is based on the Kaplan-Meier estimate.</td>
</tr>
</tbody>
</table>
PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients.

Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma: 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.
An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

### Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/dex (N=351)</th>
<th>Hazard ratio [95% CI], p-value a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression Median [95% CI], weeks</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
<tr>
<td>Progression free survival Median [95% CI], weeks</td>
<td>48.1 [36.4, 62.1]</td>
<td>20.0 [16.1, 20.1]</td>
<td>0.393 [0.326, 0.473], p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td>164.3 [145.1, 192.6]</td>
<td>136.4 [113.1, 161.7]</td>
<td>0.833 [0.687, 1.009], p = 0.045</td>
</tr>
<tr>
<td>1-year Overall survival rate</td>
<td>82%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td></td>
<td></td>
<td>Odds ratio [95% CI], p-value b</td>
</tr>
<tr>
<td>Overall response [n, %]</td>
<td>212 (60.1)</td>
<td>75 (21.4)</td>
<td>5.53 [3.97, 7.71], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete response [n, %]</td>
<td>58 (16.4)</td>
<td>11 (3.1)</td>
<td>6.08 [3.13, 11.80], p &lt; 0.001</td>
</tr>
</tbody>
</table>

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

### Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid
response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 7: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MDS-004 N = 205</th>
<th>MDS-003 N = 148</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg N = 69</td>
<td>5 mg †† N = 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion Independence (≥ 182 days) #</td>
<td>38 (55.1%)</td>
<td>24 (34.8%)</td>
</tr>
<tr>
<td>Transfusion Independence (≥ 56 days)  †</td>
<td>42 (60.9%)</td>
<td>33 (47.8%)</td>
</tr>
<tr>
<td>Median Time to Transfusion Independence (weeks)</td>
<td>4.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Median Duration of Transfusion Independence (weeks)</td>
<td>NR*</td>
<td>NR</td>
</tr>
<tr>
<td>Median Increase in Hgb, g/dL</td>
<td>6.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
# Associated with an increase in Hgb of ≥ 1 g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption

Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (Cmax) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

Distribution

In vitro (14C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

Biotransformation and elimination

Results from human in vitro metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor in vivo, though it has no inhibitory effect at in vitro concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.
Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxylenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

**Older people**

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

**Renal impairment**

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

**Hepatic impairment**

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

**Other intrinsic factors**

Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

### 5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant
toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)
Yellow iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 7 or 21 capsules. Not all pack sizes may be available.
6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/07/391/005
EU/1/07/391/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 147 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White capsules, size 2, 18.0 mm, marked “REV 5 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Newly diagnosed multiple myeloma

*Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant*

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.
**Recommended dose**

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10^9/L</td>
<td>Stop lenalidomide dosing for remainder of cycle^a</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10^9/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

^a If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level once daily</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).
Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

**Recommended dose**

The recommended starting dose of lenalidomide is 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Lenalidomide</th>
<th>Melphalan</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mg*</td>
<td>0.18 mg/kg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>7.5 mg</td>
<td>0.14 mg/kg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>5 mg</td>
<td>0.10 mg/kg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

*If neutropenia is the only toxicity at any dose level, add granulocyte stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 25 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x 10^9/L</td>
<td>Resume lenalidomide and melphalan at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily.</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L*</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

*If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.

In case of neutropenia, the use of growth factors in patient management should be considered.

**Multiple myeloma with at least one prior therapy**

**Recommended dose**

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of
each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

**Dose reduction steps**

| Starting dose | 25 mg |
| Dose level -1 | 15 mg |
| Dose level -2 | 10 mg |
| Dose level -3 | 5 mg |

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the physician should consider the use of growth factors in patient management.

**Myelodysplastic syndromes**

Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L and/or platelet counts < 25 x 10^9/L.

**Recommended dose**
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

**Recommended dose adjustments during treatment and restart of treatment**
Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reduction steps

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mg once daily on days 1-21 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Dose level -1</td>
<td>5.0 mg once daily on days 1-28 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Dose level -2</td>
<td>2.5 mg once daily on days 1-28 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Dose level -3</td>
<td>2.5 mg every other day 1-28 every 28 days</td>
<td></td>
</tr>
</tbody>
</table>

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

Thrombocytopenia

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x $10^9$/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x $10^9$/L - &lt; 50 x $10^9$/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x $10^9$/L at any time</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

Neutropenia

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 0.5 x $10^9$/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x $10^9$/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

All patients

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

Older people

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).
Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

No dose adjustment is proposed for patients older than 75 years who are treated with lenalidomide in combination with melphalan and prednisone.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years (see section 4.4).

Multiple myeloma with at least one prior therapy

The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma or myelodysplastic syndromes. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

Multiple myeloma

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily¹</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily²</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

¹ The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

² In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.
- **Myelodysplastic syndromes**

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate renal impairment</strong> (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>Starting dose 5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg once daily (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg once every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td><strong>Severe renal impairment</strong> (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td><strong>End Stage Renal Disease (ESRD)</strong> (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td><strong>On dialysis days, the dose should be administered following dialysis.</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Patients with hepatic impairment*

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

**Method of administration**

Oral use.

Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

**4.4 Special warnings and precautions for use**

*Pregnancy warning*

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.
Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
• Medroxyprogesterone acetate depot
• Tubal sterilisation
• Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
• Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected
teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Neutropenia and thrombocytopenia

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and
haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6% in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8). Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p-treated patients compared to 0.0% in MPp+p-treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p-treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8, Haemorrhagic disorders).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Myelodysplastic syndromes
Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (e.g., cough, fever, etc) thereby allowing for early management to reduce severity.

Renal impairment
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

Tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Second primary malignancies
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.
In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

**Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS**

- **Karyotype**
  
  Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- **TP53 status**
  
  A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

**Hepatic disorders**

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.
Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

Newly diagnosed multiple myeloma patients
There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min (see section 4.2 and 4.8).

Cataract
Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

Warfarin
Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin
Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%–28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.
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Statins
There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).

Interactions with P-glycoprotein (P-gp) inhibitors

In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg).

Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility

A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.
4.8  Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:
- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:
- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).
The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3−4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Common Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
</tr>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Uncommon Basal cell carcinoma Squamous skin cancer^*</td>
<td>Common Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
</tr>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Very Common Neutropenia^, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenias</td>
<td>Very Common Neutropenia^, Thrombocytopenia ^, Anaemia, Leucopenias</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Common Febrile neutropenia, Pancytopenia</td>
<td>Common Febrile neutropenia^, Pancytopenia</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Uncommon Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Uncommon Hypercoagulation, Coagulopathy</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Uncommon Hypersensitivity^</td>
<td></td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
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<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Common Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td>Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Very Common Depression, Insomnia Uncommon Loss of libido</td>
<td>Common Depression, Insomnia</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired</td>
<td>Common Cerebrovascular accident, Dizziness, Syncope Uncommon Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Very Common Cataracts, Blurred vision Common Reduced visual acuity</td>
<td>Common Cataract Uncommon Blindness</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td>Common Deafness (Including Hypoacusis), Tinnitus</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common Atrial fibrillation, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td>Common Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Hypotension, Hypertension, Ecchymosis^</td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Dyspnoea, Epistaxis^</td>
<td>Common Respiratory distress, Dyspnoea</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry mouth, Stomatitis, Dysphagia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colitis, Caecitis</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic failure^</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rashes, Pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin discoloration, Photosensitivity reaction</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscular weakness, Joint swelling, Myalgia</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure (including acute)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haematuria^, Urinary retention, Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acquired Fanconi syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest pain, Lethargy</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-reactive protein increased</td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fall, Contusion^</td>
<td></td>
</tr>
</tbody>
</table>

^See section 4.8 description of selected adverse reactions

* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls
Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3−4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Very Common Pneumonia, Common Bacterial, viral and fungal infections (including opportunistic infections)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common Thrombocytopenia, Neutropenia, Leucopenias</td>
<td>Very Common Thrombocytopenia, Neutropenia, Leucopenias Common Febrile Neutropenia</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common Decreased appetite Common Iron overload, Weight decreased</td>
<td>Common Hyperglycaemia, Decreased appetite</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Common Altered mood</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common Dizziness, Headache Common Paraesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common Acute myocardial infarction, Atrial fibrillation, Cardiac failure</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common Hypertension, Haematoma</td>
<td>Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Epistaxis</td>
<td>Common Bronchitis</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation</td>
<td>Common Diarrhoea¹, Nausea, Toothache</td>
</tr>
<tr>
<td></td>
<td>Common Dry mouth, Dyspepsia</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common Abnormal liver function tests</td>
<td>Common Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common Rashes, Dry Skin, Pruritus</td>
<td>Common Rashes, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td>Common Back pain²</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome</td>
<td>Common Pyrexia</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome</td>
<td>Common Pyrexia</td>
</tr>
<tr>
<td></td>
<td>o All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Myelodysplastic syndromes Phase II study</strong></td>
<td>o All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects</td>
<td></td>
</tr>
<tr>
<td><strong>Algorithm applied for inclusion in the SmPC:</strong></td>
<td>All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.</td>
<td></td>
</tr>
</tbody>
</table>

*See section 4.8 description of selected adverse reactions

¹ Adverse events reported as serious in myelodysplastic syndromes clinical trials

Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event

# Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo

- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
</table>

#### Neoplasms
- **Benign, Malignant and Unspecified (incl cysts and polyps)**
  - Rare
  - Tumour lysis syndrome

#### Endocrine Disorders
- **Common**
  - Hyperthyroidism

#### Respiratory, Thoracic and Mediastinal Disorders
- **Not Known**
  - Interstitial pneumonitis

#### Gastrointestinal Disorders
- **Not Known**
  - Pancreatitis

#### Hepatobiliary Disorders
- **Not Known**
  - Acute hepatic failure, Hepatitis toxic, Cytolytic hepatitis, Cholestatic hepatitis, Mixed cytolytic/cholestatic hepatitis

#### Skin and Subcutaneous Tissue Disorders
- **Uncommon**
  - Angioedema
  - Stevens-Johnson Syndrome, Toxic epidermal necrolysis
  - Not Known
  - Leukocytoclastic vasculitis

---

**Description of selected adverse reactions**

**Teratogenicity**

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

**Neutropenia and thrombocytopenia**

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone**

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared...
with 7.8% in MPP+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPP+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPP+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**

An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone or as monotherapy in patients with myelodysplastic syndromes treated with lenalidomide monotherapy (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**
*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

**Acute myeloid leukaemia**

- **Multiple myeloma**

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- **Myelodysplastic syndromes**

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

**Hepatic disorders**

The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Rhabdomyolysis**

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

**Thyroid disorders**

Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

**Gastrointestinal disorders**

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

There is no specific experience in the management of lenalidomide overdose in patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation
The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

Table 4: Summary of overall efficacy data

<table>
<thead>
<tr>
<th></th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed PFS – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median^a PFS time, months (95% CI)^b</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]^c; p-value^d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS2^e – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median^a PFS time, months (95% CI)^b</td>
<td>42.9 (38.1, 47.4)</td>
<td>40.0 (36.2, 44.2)</td>
<td>35.0 (30.4, 37.8)</td>
</tr>
<tr>
<td>HR [95% CI]^c; p-value^d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median^a OS time, months (95% CI)^b</td>
<td>58.9 (56.0, NE)</td>
<td>56.7 (50.1, NE)</td>
<td>48.5 (44.2, 52.0)</td>
</tr>
<tr>
<td>HR [95% CI]^c; p-value^d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.91 (0.75, 1.09); 0.305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.83 (0.69, 0.99); 0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median^ (min, max): all patients</td>
<td>40.8 (0.0, 65.9)</td>
<td>40.1 (0.4, 65.7)</td>
<td>38.7 (0.0, 64.2)</td>
</tr>
</tbody>
</table>
The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3-arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5:

Table 5: Summary of overall efficacy data

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>MPR+R (N = 152)</th>
<th>MPR+p (N = 153)</th>
<th>MPp+p (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median* PFS time, months (95% CI)</td>
<td>27.4 (21.3, 35.0)</td>
<td>14.3 (13.2, 15.7)</td>
<td>13.1 (12.0, 14.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
<td>0.37 (0.27, 0.50); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
<td>0.47 (0.35, 0.65); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
<td>0.78 (0.60, 1.01); 0.059</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MPR+R (N = 152) | MPR+p (N = 153) | MPp +p (N = 154)
---|---|---
PFS2 — (months)² | | |
Median⁴ PFS time, months (95% CI) | 39.7 (29.2, 48.4) | 27.8 (23.1, 33.1) | 28.8 (24.3, 33.8)
HR [95% CI]; p-value | | | |
MPR+R vs MPp+p | 0.70 (0.54, 0.92); 0.009 | | |
MPR+R vs MPR+p | 0.77 (0.59, 1.02); 0.065 | | |
MPR+p vs MPp +p | 0.92 (0.71, 1.19); 0.051 | | |
Overall survival (months) | | | |
Median⁴ OS time, months (95% CI) | 55.9 (49.1, 67.5) | 51.9 (43.1, 60.6) | 53.9 (47.3, 64.2)
HR [95% CI]; p-value | | | |
MPR+R vs MPp+p | 0.95 (0.70, 1.29); 0.736 | | |
MPR+R vs MPR+p | 0.88 (0.65, 1.20); 0.43 | | |
MPR+p vs MPp +p | 1.07 (0.79, 1.45); 0.67 | | |
Follow-up (months) | | | |
Median (min, max): all patients | 48.4 (0.8, 73.8) | 46.3 (0.5, 71.9) | 50.4 (0.5, 73.3)
Investigator-assessed Myeloma response n (%) | | | |
CR | 30 (19.7) | 17 (11.1) | 9 (5.8)
PR | 90 (59.2) | 99 (64.7) | 75 (48.7)
Stable Disease (SD) | 24 (15.8) | 31 (20.3) | 63 (40.9)
Response Not Evaluable (NE) | 8 (5.3) | 4 (2.6) | 7 (4.5)
Investigator-assessed Duration of response (CR+PR) — (months) | | | |
Median⁴ (95% CI) | 26.5 (19.4, 35.8) | 12.4 (11.2, 13.9) | 12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

*The median is based on the Kaplan-Meier estimate
²PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients

**Supportive newly diagnosed multiple myeloma studies**
An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/ low dose dexamethasone tends to decrease.
Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).
Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex  (N=353)</th>
<th>placebo/dex  (N=351)</th>
<th>Hazard ratio [95% CI], p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression free survival</td>
<td>48.1 [36.4, 62.1]</td>
<td>20.0 [16.1, 20.1]</td>
<td>0.393 [0.326, 0.473], p &lt; 0.001</td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>164.3 [145.1, 192.6]</td>
<td>136.4 [113.1, 161.7]</td>
<td>0.833 [0.687, 1.009], p = 0.045</td>
</tr>
<tr>
<td>1-year Overall survival rate</td>
<td>82%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response [n, %]</td>
<td>212 (60.1)</td>
<td>75 (21.4)</td>
<td>5.53 [3.97, 7.71], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete response [n, %]</td>
<td>58 (16.4)</td>
<td>11 (3.1)</td>
<td>6.08 [3.13, 11.80], p &lt; 0.001</td>
</tr>
<tr>
<td>Odds ratio [95% CI], p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Two-tailed log rank test comparing survival curves between treatment groups.
<sup>b</sup> Two-tailed continuity-corrected chi-square test.

Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 7: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

| Endpoint                          | MDS-004  
|                                  | N = 205 |                                  | MDS-003 
|                                  | N = 148 |
|                                  | 10 mg  | 5 mg<sup>†</sup> | Placebo<sup>‡</sup> | 10 mg  |
|                                  | N = 69 | N = 69 | N = 67 | N = 148 |
| Transfusion Independence          | 38 (55.1%) | 24 (34.8%) | 4 (6.0%) | 86 (58.1%) |
| (≥ 182 days)<sup>§</sup>         |        |        |        |        |
Transfusion Independence (≥ 56 days)  

<table>
<thead>
<tr>
<th></th>
<th>42 (60.9%)</th>
<th>33 (47.8%)</th>
<th>5 (7.5%)</th>
<th>97 (65.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to Transfusion Independence (weeks)</td>
<td>4.6</td>
<td>4.1</td>
<td>0.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Median Duration of Transfusion Independence (weeks)</td>
<td>NR†</td>
<td>NR</td>
<td>NR</td>
<td>114.4</td>
</tr>
<tr>
<td>Median Increase in Hgb, g/dL</td>
<td>6.4</td>
<td>5.3</td>
<td>2.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles  
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles  
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase  
† Associated with an increase in Hgb of ≥ 1 g/dL  
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption

Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_max) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.
Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

**Distribution**

*In vitro* (\(^{14}\)C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

**Biotransformation and elimination**

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

*In vitro* studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor *in vivo*, though it has no inhibitory effect at *in vitro* concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

**Older people**

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

**Renal impairment**

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance
measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

**Hepatic impairment**

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

**Other intrinsic factors**

Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

### 5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrioventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

*In vitro* (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.
6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Capsule contents**
- Lactose, anhydrous
- Cellulose, microcrystalline
- Croscarmellose sodium
- Magnesium stearate

**Capsule shell**
- Gelatin
- Titanium dioxide (E171)

**Printing ink**
- Shellac
- Propylene glycol
- Black iron oxide (E172)
- Potassium hydroxide

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 7 or 21 capsules. Not all pack sizes may be available.

6.6 **Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

7. **MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/001
9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14 June 2007  
Date of latest renewal: 14 June 2012

10. **DATE OF REVISION OF THE TEXT**

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 7.5 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 144.5 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pale yellow/white capsules, size 2, 18.0 mm, marked “REV 7.5 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

Newly diagnosed multiple myeloma

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Dose reduction</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10⁹/L</td>
<td>Stop lenalidomide dosing for remainder of cycle</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10⁹/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

*If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10⁹/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

**Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant**

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.5 x 10⁹/L, and/or platelet counts are < 75 x 10⁹/L.

**Recommended dose**

The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

**Recommended dose adjustments during treatment and restart of treatment:**

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reduction steps

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Melphalan</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mgª</td>
<td>0.18 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>7.5 mg</td>
<td>0.14 mg/kg</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>5 mg</td>
<td>0.10 mg/kg</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>2.5 mg</td>
<td>NA</td>
<td>0.25 mg/kg</td>
</tr>
</tbody>
</table>

ª If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

Thrombocytopenia

When platelets

| First fall to < 25 x 10^9/L | Interrupt lenalidomide treatment |
| Return to ≥ 25 x 10^9/L     | Resume lenalidomide and melphalan at Dose level -1 |

| For each subsequent drop below 30 x 10^9/L | Interrupt lenalidomide treatment |
| Return to ≥ 30 x 10^9/L                   | Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. |

Neutropenia

When neutrophils

| First fall to < 0.5 x 10^9/Lª | Interrupt lenalidomide treatment |
| Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity | Resume lenalidomide at Starting dose once daily |

| Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed | Resume lenalidomide at Dose level -1 once daily |

| For each subsequent drop below < 0.5 x 10^9/L | Interrupt lenalidomide treatment |
| Return to ≥ 0.5 x 10^9/L | Resume lenalidomide at next lower dose level once daily. |

ª If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only Dose Limiting Toxicity (DLT). Otherwise, decrease by one dose level at start of next cycle.

In case of neutropenia, the use of growth factors in patient management should be considered.

Multiple myeloma with at least one prior therapy

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reduction steps

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>15</td>
</tr>
<tr>
<td>-2</td>
<td>10</td>
</tr>
<tr>
<td>-3</td>
<td>5</td>
</tr>
</tbody>
</table>

Thrombocytopenia

When platelets | Recommended course
---|-------------------
First fall to < 30 x 10^9/L | Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L | Resume lenalidomide at Dose level -1
For each subsequent drop below 30 x 10^9/L | Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L | Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.

Neutropenia

When neutrophils | Recommended course
---|-------------------
First fall to < 0.5 x 10^9/L | Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity | Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed | Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L | Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L | Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.

In case of neutropenia, the use of growth factors in patient management should be considered.

All patients
For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population
Revlidim should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

Older people
Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).
Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years treated with lenalidomide in combination with melphalan and prednisone.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years (see section 4.4).

Multiple myeloma with at least one prior therapy

The percentage of patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily¹</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily² 15 mg every other day</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

¹ The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.
² In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

Patients with hepatic impairment

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Method of administration

Oral use.
Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:
- Age ≥ 50 years and naturally amenorrheic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.

Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.
Follow-up and end of treatment
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy,
should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

**Neutropenia and thrombocytopenia**

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 (treatment for 18 four-week cycles) compared with 15% in the melphalan/prednisonethalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6% in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisonethalidomide arm, see section 4.8. Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively; Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in case of concomitant medicinal products susceptible to induce bleeding (see section 4.8 Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPP+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0% in MPP+p treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPP+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8, Haemorrhagic disorders).
Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Renal impairment
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

Tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.
Lactose intolerance
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Second primary malignancies
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytoytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or
concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min (see section 4.2 and 4.8).

**Cataract**

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

**4.5 Interaction with other medicinal products and other forms of interaction**

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

**Statins**

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

**Dexamethasone**

Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).

**Interactions with P-glycoprotein (P-gp) inhibitors**

*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate
Temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:
  - Pneumonia (9.8%)
  - Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).
Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan, prednisone and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were:

- Neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism).
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia.

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Common Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Basal cell carcinoma, Squamous skin cancer^*</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Basal cell carcinoma, Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Neutropenia^, Thrombocytopenia^, Anaemia, Haemorrhagic disorder^, Leucopenias</td>
<td>Very Common Neutropenia^, Thrombocytopenia^, Anaemia, Leucopenias</td>
</tr>
<tr>
<td>Common</td>
<td>Febrile neutropenia, Pancytopenia</td>
<td>Common Febrile neutropenia^, Pancytopenia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Uncommon Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Uncommon Hypersensitivity^</td>
<td>Hypercoagulation, Coagulopathy</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Common Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
<td>Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td>Common</td>
<td>Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Very Common Depression, Insomnia</td>
<td>Common Depression, Insomnia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Loss of libido</td>
<td></td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3−4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache</td>
<td>Cerebrovascular accident, Dizziness, Syncope</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Ataxia, Balance impaired</td>
<td>Intracranial haemorrhage, Transient ischaemic attack, Cerebral ischaemia</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Cataracts, Blurred vision</td>
<td>Cataract</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Reduced visual acuity</td>
<td>Blindness</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Deafness (Including Hypoacusis), Tinnitus</td>
<td>Myocardial infarction (including acute), Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation, Bradycardia</td>
<td>Myocardial infarction, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypotension, Hypertension, Ecchymosis</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea, Epistaxis</td>
<td>Respiratory distress, Dyspnoea</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia</td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)</td>
<td>Cholestasis, Abnormal liver function tests, Hepatic failure</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colitis, Caecitis</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
<td>Cholestasis, Abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discoloration, Photosensitivity reaction</td>
<td>Common Rashes</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia Common Muscular weakness, Joint swelling, Myalgia</td>
<td>Common Muscular weakness, Bone pain Uncommon Joint swelling</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Very Common Renal failure (including acute) Common Haematuria^, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome</td>
<td>Uncommon Renal tubular necrosis</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Common Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy</td>
<td>Common Fatigue, Pyrexia, Asthenia</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common C-reactive protein increased</td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>Common Fall, Contusion^</td>
<td></td>
</tr>
</tbody>
</table>

^See section 4.8 description of selected adverse reactions

* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.
Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Pneumonia(^\diamond)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia(^\wedge), Neutropenia(^\wedge), Leucopenias</td>
<td>Thrombocytopenia(^\wedge), Neutropenia(^\wedge), Leucopenias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile Neutropenia(^\wedge)</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Hyperglycaemia(^\wedge), Decreased appetite</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>Hyperglycaemia(^\wedge), Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Iron overload, Weight decreased</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altered mood(^\wedge)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dizziness, Headache</td>
<td>Acute myocardial infarction(^\wedge), Atrial fibrillation(^\wedge), Cardiac failure(^\wedge)</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism(^\wedge)</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchitis</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypertension, Haematoma</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism(^\wedge)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Epistaxis(^\wedge)</td>
<td>Bronchitis</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation</td>
<td>Diarrhoea(^\wedge), Nausea, Toothache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dry mouth, Dyspepsia</td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rashes, Dry Skin, Pruritus</td>
<td>Rashes, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td>Back pain(^\wedge)</td>
</tr>
</tbody>
</table>
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Common Renal failure</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Common Fall</td>
</tr>
</tbody>
</table>

### Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Common Hyperthyroidism</td>
<td>Rare Tumour lysis syndrome</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td>Not Known Interstitial pneumonitis</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td>Not Known Pancreatitis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th></th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td>Not Known</td>
<td>Not Known</td>
</tr>
<tr>
<td><strong>Disorders</strong></td>
<td>Acute hepatic failure^, Hepatitis toxic^,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytoytic hepatitis^, Cholestatic hepatitis^, Mixed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cytoytic/cholestatic hepatitis^</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon, Angioedema, Rare, Stevens-Johnson Syndrome^,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxic epidermal necrolysis^,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocytoclastic vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

*see section 4.8 description of selected adverse reactions

### Description of selected adverse reactions

#### Teratogenicity

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

#### Neutropenia and thrombocytopenia

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone**

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo. Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**
SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**
*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

**Acute myeloid leukaemia**
- **Multiple myeloma**

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- **Myelodysplastic syndromes**

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality.
compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

**Hepatic disorders**
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Rhabdomyolysis**
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

**Thyroid disorders**
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

**Gastrointestinal disorders**
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

There is no specific experience in the management of lenalidomide overdose in multiple myeloma patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

**Mechanism of action**
The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.
Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

**Newly diagnosed multiple myeloma**

*Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation*

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CL\text{cr}] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

**Table 4: Summary of overall efficacy data**

<table>
<thead>
<tr>
<th></th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator-assessed PFS – (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS time, months (95% CI)(^b)</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d) Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS2(^e) – (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS time, months (95% CI)(^b)</td>
<td>42.9 (38.1, 47.4)</td>
<td>40.0 (36.2, 44.2)</td>
<td>35.0 (30.4, 37.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d) Rd vs MPT</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) OS time, months (95% CI)(^b)</td>
<td>58.9 (56.0, NE)</td>
<td>56.7 (50.1, NE)</td>
<td>48.5 (44.2, 52.0)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d) Rd vs MPT</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.91 (0.75, 1.09); 0.305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.83 (0.69, 0.99); 0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPP+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPP+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5:

**Table 5: Summary of overall efficacy data**

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>MPR+R (N = 152)</th>
<th>MPR+p (N = 153)</th>
<th>MPP+p (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS time, months (95% CI)</td>
<td>27.4 (21.3, 35.0)</td>
<td>14.3 (13.2, 15.7)</td>
<td>13.1 (12.0, 14.8)</td>
</tr>
<tr>
<td>HR [95% CI], p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPP+p</td>
<td>0.37 (0.27, 0.50); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
<td>0.47 (0.35, 0.65); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+p vs MPP+p</td>
<td>0.78 (0.60, 1.01); 0.059</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide / low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.
In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses—pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/dex (N=351)</th>
<th>Hazard ratio [95% CI], p-value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time To progression Median [95% CI], weeks</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
<tr>
<td>Progression free survival Median [95% CI], weeks</td>
<td>48.1 [36.4, 62.1]</td>
<td>20.0 [16.1, 20.1]</td>
<td>0.393 [0.326, 0.473], p &lt; 0.001</td>
</tr>
<tr>
<td>Endpoint</td>
<td>len/dex (N=353)</td>
<td>placebo/dex (N=351)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Overall survival median [95% CI], weeks</td>
<td>164.3 [145.1, 192.6]</td>
<td>136.4 [113.1, 161.7]</td>
<td>0.833 [0.687, 1.009] p = 0.045</td>
</tr>
<tr>
<td>1-year Overall survival rate</td>
<td>82%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response [n, %]</td>
<td>212 (60.1)</td>
<td>75 (21.4)</td>
<td>5.53 [3.97, 7.71], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete response [n, %]</td>
<td>58 (16.4)</td>
<td>11 (3.1)</td>
<td>6.08 [3.13, 11.80], p &lt; 0.001</td>
</tr>
</tbody>
</table>

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

**Paediatric population**

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

### 5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

**Absorption**
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C\text{\text{max}}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in C\text{\text{max}} in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

**Distribution**

\textit{In vitro} (^14C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

**Biotransformation and elimination**

Results from human \textit{in vitro} metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. \textit{In vitro} studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.
In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor in vivo, though it has no inhibitory effect at in vitro concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxylenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

Older people
No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment
The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The Cmax was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment
Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data
An embryofetal development study has been conducted in monkeys administered lenalidomide at doses
from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 21 capsules.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Revlimid 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 294 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Blue-green/pale yellow capsules, size 0, 21.7 mm, marked “REV 10 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Newly diagnosed multiple myeloma

*Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant*

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10⁹/L, and/or platelet counts are < 50 x 10⁹/L.
Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10^9/L</td>
<td>Stop lenalidomide dosing for remainder of cycle^a</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10^9/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

^a If Dose Limiting Toxicity occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^7/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10^7/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^7/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^7/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^7/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered. If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).
Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

**Recommended dose**

The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Melphalan</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mg*</td>
<td>0.18 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>7.5 mg</td>
<td>0.14 mg/kg</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>5 mg</td>
<td>0.10 mg/kg</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>2.5 mg</td>
<td>NA</td>
<td>0.25 mg/kg</td>
</tr>
</tbody>
</table>

* If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 25 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x 10^9/L</td>
<td>Resume lenalidomide and melphalan at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below 30 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L*</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level once daily</td>
</tr>
</tbody>
</table>

*If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.

In case of neutropenia, the use of growth factors in patient management should be considered.

**Multiple myeloma with at least one prior therapy**

- **Recommended dose**

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of
each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10⁹/L, and/or platelet counts < 75 x 10⁹/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10⁹/L.

**Recommended dose adjustments during treatment and restart of treatment**

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

| Starting dose | 25 mg |
| Dose level -1 | 15 mg |
| Dose level -2 | 10 mg |
| Dose level -3 | 5 mg |

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>&lt; 30 x 10⁹/L</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>For each subsequent drop below</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>30 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
<tr>
<td>Return to ≥ 30 x 10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>&lt; 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when neutropenia is the only observed toxicity</td>
<td></td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>&lt; 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

In case of neutropenia, the physician should consider the use of growth factors in patient management.

**Myelodysplastic syndromes**

Lenalidomide treatment must not be started if the ANC < 0.5 x 10⁹/L and/or platelet counts < 25 x 10⁹/L.

**Recommended dose**

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

**Recommended dose adjustments during treatment and restart of treatment**

Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reduction steps

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting</td>
<td>10 mg once daily on days 1-21 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Level -1</td>
<td>5.0 mg once daily on days 1-28 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Level -2</td>
<td>2.5 mg once daily on days 1-28 every 28 days</td>
<td></td>
</tr>
<tr>
<td>Level -3</td>
<td>2.5 mg every other day 1-28 every 28 days</td>
<td></td>
</tr>
</tbody>
</table>

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 25 x 10^9/L - &lt; 50 x 10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/L at any time</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3)</td>
</tr>
</tbody>
</table>

**Discontinuation of lenalidomide**

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

**All patients**

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

**Special populations**

**Paediatric population**

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

**Older people**

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).
Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

No dose adjustment is proposed for patients older than 75 years who are treated with lenalidomide in combination with melphalan and prednisone.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75years (see section 4.4).

Multiple myeloma with at least one prior therapy

The percentage of multiple myeloma patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma or myelodysplastic syndromes. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

Multiple myeloma

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

<sup>1</sup> The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

<sup>2</sup> In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.
- **Myelodysplastic syndromes**

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>Starting dose 5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg once daily (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg once every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>Starting dose 2.5 mg once daily (days 1-21 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -1 2.5 mg every other day (days 1-28 of repeated 28-day cycles)</td>
</tr>
<tr>
<td></td>
<td>Dose level -2 2.5 mg twice a week (days 1-28 of repeated 28-day cycles)</td>
</tr>
</tbody>
</table>

*On dialysis days, the dose should be administered following dialysis.*

**Patients with hepatic impairment**
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

**Method of administration**

**Oral use.**
Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

**4.4 Special warnings and precautions for use**

**Pregnancy warning**
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.
Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age $\geq 50$ years and naturally amenorrhoeic for $\geq 1$ year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
• Medroxyprogesterone acetate depot
• Tubal sterilisation
• Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
• Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected
teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and
haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8). Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0% in MPp+p treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in clinical trials of multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8, Haemorrhagic disorders).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Myelodysplastic syndromes
Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

*Infection with or without neutropenia*
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

*Renal impairment*
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

*Thyroid disorders*
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

*Peripheral neuropathy*
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

*Tumour lysis syndrome*
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

*Allergic reactions*
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

*Severe skin reactions*
SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

*Lactose intolerance*
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

*Unused capsules*
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

*Second primary malignancies*
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.
In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

**Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS**

- **Karyotype**
  Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- **TP53 status**
  A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

**Hepatic disorders**
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytoytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.
Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min (see section 4.2 and 4.8).

**Cataract**

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

**4.5 Interaction with other medicinal products and other forms of interaction**

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.
Statins
There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg/day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/day).

Interactions with P-glycoprotein (P-gp) inhibitors
*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines
Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.
4.8 Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+ p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).
The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Common</td>
<td>Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis, Sinusitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous skin cancer**</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Neutropenia*, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenias</td>
<td>Neutropenia*, Thrombocytopenia ^, Anaemia, Leucopenias</td>
<td>Neutropenia*, Thrombocytopenia ^, Anaemia, Leucopenias</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia, Pancytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypercoagulation, Coagulopathy</td>
<td></td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3−4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity^</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Very Common</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Very Common</td>
<td>Depression, Insomnia</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Very Common</td>
<td>Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Loss of libido</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Ataxia, Balance impaired</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Very Common</td>
<td>Cataracts, Blurred vision</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Reduced visual acuity</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Deafness (Including Hypoacusis), Tinnitus</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Common</td>
<td>Atrial fibrillation, Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Very Common</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Hypotension, Hypertension, Ecchymosis^</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Very Common</td>
<td>Dyspnoea, Epistaxis^</td>
</tr>
</tbody>
</table>
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia</td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry mouth, Stomatitis, Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Colitis, Caecitis</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>Cholestasis, Abnormal liver function tests</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic failure^</td>
<td>Hepatic failure^</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common</td>
</tr>
<tr>
<td>Rashes, Pruritus</td>
<td>Rashes</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Skin discoulouration, Photosensitivity reaction</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common</td>
</tr>
<tr>
<td>Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia</td>
<td>Muscular weakness, Bone pain</td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Muscular weakness, Joint swelling, Myalgia</td>
<td>Joint swelling</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Very Common</td>
</tr>
<tr>
<td>Renal failure (including acute)</td>
<td>Renal tubular necrosis</td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haematuria^, Urinary retention, Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Acquired Fanconi syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Common</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Very Common</td>
</tr>
<tr>
<td>Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors)</td>
<td>Fatigue, Pyrexia, Asthenia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Chest pain, Lethargy</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>Common</td>
</tr>
<tr>
<td>Fall, Contusion^</td>
<td></td>
</tr>
</tbody>
</table>

^See section 4.8 description of selected adverse reactions
* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls
Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Very Common</td>
<td>Very Common Pneumonia◊</td>
</tr>
<tr>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Common Bacterial, viral and fungal infections (including opportunistic infections) ◊</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Very Common</td>
<td>Very Common Pneumonia◊</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia◊, Neutropenia◊, Leucopenias</td>
<td>Thrombocytopenia◊, Neutropenia◊, Leucopenias</td>
</tr>
<tr>
<td></td>
<td>Common Febrile Neutropenia◊^</td>
<td></td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Very Common</td>
<td>Common Hyperglycaemia◊, Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Very Common</td>
<td>Common Hyperglycaemia◊, Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common Iron overload, Weight decreased</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Common</td>
<td>Common Altered mood◊</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Very Common</td>
<td>Common Acute myocardial infarction◊, Atrial fibrillation◊, Cardiac failure◊</td>
</tr>
<tr>
<td></td>
<td>Dizziness, Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common Paraesthesia</td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Common</td>
<td>Common Acute myocardial infarction◊, Atrial fibrillation◊, Cardiac failure◊</td>
</tr>
<tr>
<td></td>
<td>Hypertension, Haematoma</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism◊</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension, Haematoma</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Very Common</td>
<td>Common Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Epistaxis◊</td>
<td></td>
</tr>
</tbody>
</table>
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td><strong>Common</strong> Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation <strong>Common</strong> Dry mouth, Dyspepsia</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td><strong>Common</strong> Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td><strong>Very Common</strong> Rashes, Dry Skin, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td><strong>Very Common</strong> Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td><strong>Very Common</strong> Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
</tr>
</tbody>
</table>

^1 Adverse events reported as serious in myelodysplastic syndromes clinical trials ^6 Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event

**Algorithm applied for myelodysplastic syndromes:**
- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

**Tabulated summary of post-marketing adverse reactions**

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

**Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide**

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
</table>

121
<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td></td>
<td>Rare Tumour lysis syndrome</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Not Known Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Not Known</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Not Known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^</td>
<td>Not Known Acute hepatic failure^, Hepatitis toxic^</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Uncommon Angioedema Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ Not Known</td>
<td>Leukocytoclastic vasculitis</td>
</tr>
</tbody>
</table>

^see section 4.8 description of selected adverse reactions

**Description of selected adverse reactions**

**Teratogenicity**

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

**Neutropenia and thrombocytopenia**

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone**

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).
The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**

An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**

*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.*
Acute myeloid leukaemia

- Multiple myeloma

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- Myelodysplastic syndromes

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders

The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Thyroid disorders

Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

Gastrointestinal disorders

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

Mechanism of action
The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety
Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:
Table 4: Summary of overall efficacy data

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median* PFS time, months (95% CI)b</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]c; p-valued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS2* – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median* PFS time, months (95% CI)b</td>
<td>42.9 (38.1, 47.4)</td>
<td>40.0 (36.2, 44.2)</td>
<td>35.0 (30.4, 37.8)</td>
</tr>
<tr>
<td>HR [95% CI]c; p-valued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median* OS time, months (95% CI)b</td>
<td>58.9 (56.0, NE)</td>
<td>56.7 (50.1, NE)</td>
<td>48.5 (44.2, 52.0)</td>
</tr>
<tr>
<td>HR [95% CI]c; p-valued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.91 (0.75, 1.09); 0.305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.83 (0.69, 0.99); 0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median* (min, max): all patients</td>
<td>40.8 (0.0, 65.9)</td>
<td>40.1 (0.4, 65.7)</td>
<td>38.7 (0.0, 64.2)</td>
</tr>
<tr>
<td>Myeloma responsee n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>81 (15.1)</td>
<td>77 (14.2)</td>
<td>51 (9.3)</td>
</tr>
<tr>
<td>VGPR</td>
<td>152 (28.4)</td>
<td>154 (28.5)</td>
<td>103 (18.8)</td>
</tr>
<tr>
<td>PR</td>
<td>169 (31.6)</td>
<td>166 (30.7)</td>
<td>187 (34.2)</td>
</tr>
<tr>
<td>Overall response: CR, VGPR, or PR</td>
<td>402 (75.1)</td>
<td>397 (73.4)</td>
<td>341 (62.3)</td>
</tr>
<tr>
<td>Duration of response – (months)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median* (95% CI)f</td>
<td>35.0 (27.9, 43.4)</td>
<td>22.1 (20.3, 24.0)</td>
<td>22.3 (20.2, 24.9)</td>
</tr>
</tbody>
</table>

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio;
IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum;
m = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response;
R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≥18 cycles; SE = standard error;
T = thalidomide; VGPR = very good partial response; vs = versus.

* The median is based on the Kaplan-Meier estimate.
* The 95% CI about the median.
* Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
* The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
Exploratory endpoint (PFS2)
* The median is the univariate statistic without adjusting for censoring.
* Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category. Data cutoff date = 24 May 2013).
* data cut 24 May 2014

Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance
monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5

<table>
<thead>
<tr>
<th>Table 5: Summary of overall efficacy data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Investigator-assessed PFS — (months)</td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td>PFS2 — (months)</td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
</tr>
<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td>Overall survival (months)</td>
</tr>
<tr>
<td>Median OS time, months (95% CI)</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
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<tr>
<td>MPR+p vs MPp+p</td>
</tr>
<tr>
<td>Follow-up (months)</td>
</tr>
<tr>
<td>Median (min, max): all patients</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>Investigator-assessed Myeloma response n (€)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
</tr>
<tr>
<td>Response Not Evaluable (NE)</td>
</tr>
<tr>
<td>Investigator-assessed Duration of response (CR+PR) — (months)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>MPR+R (N = 152)</td>
</tr>
<tr>
<td>MPR+p (N = 153)</td>
</tr>
<tr>
<td>MPp+p (N = 154)</td>
</tr>
<tr>
<td>CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.</td>
</tr>
<tr>
<td>*The median is based on the Kaplan-Meier estimate</td>
</tr>
<tr>
<td>#(PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients</td>
</tr>
</tbody>
</table>

Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm...
received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide/ low dose dexamethasone tends to decrease.

**Multiple myeloma with at least one prior therapy**

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm.
in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009]). p=0.045).

Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/dex (N=351)</th>
<th>Hazard ratio [95% CI], p-value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression free survival</td>
<td>48.1 [36.4, 62.1]</td>
<td>20.0 [16.1, 20.1]</td>
<td>0.393 [0.326, 0.473], p &lt; 0.001</td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>164.3 [145.1, 192.6]</td>
<td>136.4 [113.1, 161.7]</td>
<td>0.833 [0.687, 1.009], p = 0.045</td>
</tr>
<tr>
<td>Median [95% CI], weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year Overall survival rate</td>
<td>82%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response [n, %]</td>
<td>212 (60.1)</td>
<td>75 (21.4)</td>
<td>5.53 [3.97, 7.71], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete response [n, %]</td>
<td>58 (16.4)</td>
<td>11 (3.1)</td>
<td>6.08 [3.13, 11.80], p &lt; 0.001</td>
</tr>
</tbody>
</table>

a: Two-tailed log rank test comparing survival curves between treatment groups.

b: Two-tailed continuity-corrected chi-square test.

Myelodysplastic syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.
Table 7: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MDS-004 N = 205</th>
<th>MDS-003 N = 148</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg N = 69</td>
<td>5 mg †† N = 69</td>
</tr>
<tr>
<td>Transfusion Independence (≥ 182 days) #</td>
<td>38 (55.1%)</td>
<td>24 (34.8%)</td>
</tr>
<tr>
<td>Transfusion Independence (≥ 56 days) †</td>
<td>42 (60.9%)</td>
<td>33 (47.8%)</td>
</tr>
<tr>
<td>Median Time to Transfusion Independence (weeks)</td>
<td>4.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Median Duration of Transfusion Independence (weeks)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median Increase in Hgb, g/dL</td>
<td>6.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
# Associated with an increase in Hgb of ≥ 1 g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties
Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.
Absorption
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration ($C_{\text{max}}$) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in $C_{\text{max}}$ in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

Distribution
In vitro ($^{14}$C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

Biotransformation and elimination
Results from human in vitro metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor in vivo, though it has no inhibitory effect at in vitro concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxylenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.
Older people

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The Cmax was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors

Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrioventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.
In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)
Yellow iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 21 capsules.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Revlimid 15 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 15 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 289 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pale blue/white capsules, size 0, 21.7 mm, marked “REV 15 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

Newly diagnosed multiple myeloma

*Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant*

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is $< 1.0 \times 10^9/L$, and/or platelet counts are $< 50 \times 10^9/L$.

Recommended dose
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients $\geq 75$ years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.
Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Dose reduction steps</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10⁹/L</td>
<td>Stop lenalidomide dosing for remainder of cycle&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10⁹/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

<sup>a</sup> If Dose Limiting Toxicity occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10⁹/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10⁹/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10⁹/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered. If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

**Multiple myeloma with at least one prior therapy**

**Recommended dose**

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10⁹/L, and/or platelet counts < 75 x 10⁹/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10⁹/L.
Recommended dose adjustments during treatment and restart of treatment

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level -1</td>
<td>15 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>10 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to $&lt; 30 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 30 \times 10^9/L$</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below $30 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 30 \times 10^9/L$</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to $&lt; 0.5 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$ when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below $&lt; 0.5 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

**All patients**

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to $\leq$ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

**Special populations**

**Paediatric population**

Revlímid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

**Older people**

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).
In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

- Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in the patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years. (see Section 4.4).

- Multiple myeloma with at least one prior therapy

The percentage of patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

**Patients with renal impairment**

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis).

- **Multiple myeloma**

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily¹</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily² 15 mg every other day</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

¹ The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

² In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

**Patients with hepatic impairment**

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.
Method of administration

Oral use.

Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy warning

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling

For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential

Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.

Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective
contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

**Follow-up and end of treatment**
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

**Men**
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

**Additional precautions**
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

**Educational materials, prescribing and dispensing restrictions**
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

**Other special warnings and precautions for use**

**Cardiovascular disorders**

**Myocardial infarction**
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

**Venous and arterial thromboembolic events**
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking,
hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8. Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in
patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8 Haemorrhagic disorders).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

**Infection with or without neutropenia**

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

**Renal impairment**

Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

**Thyroid disorders**

Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

**Peripheral neuropathy**

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

**Tumour lysis syndrome**

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction
depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Second primary malignancies
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.
Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS ≤ 2 or CLcr < 60 mL/min (see section 4.2 and 4.8).

**Cataract**

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

### 4.5 Interaction with other medicinal products and other forms of interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

**Statins**

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

**Dexamethasone**

Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).
Interactions with P-glycoprotein (P-gp) inhibitors

*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

**Women of childbearing potential / Contraception in males and females**

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

**Pregnancy**

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

**Breast-feeding**

It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

**Fertility**

A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

**Summary of the safety profile**

*Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone*

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)
The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+ p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing
seriousness. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in the any of the main clinical trials.

**Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone**

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
</tr>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma</td>
<td>Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
</tr>
<tr>
<td></td>
<td>Squamous skin cancer^*</td>
<td>T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Neutropenia^, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenias</td>
<td>Neutropenia^, Thrombocytopenia^, Anaemia, Leucopenias</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia, Pancytopenia</td>
<td>Febrile neutropenia^, Pancytopenia, Haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity^</td>
<td>Hypercoagulation, Coagulopathy</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyperonatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td>Depression, Insomnia</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Depression, Insomnia</td>
<td>Depression, Insomnia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Loss of libido</td>
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<td></td>
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</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
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</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache</td>
<td>Cerebrovascular accident, Dizziness, Syncope</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Ataxia, Balance impaired</td>
<td>Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Cataracts, Blurred vision</td>
<td>Cataract</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Reduced visual acuity</td>
<td>Blindness</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Deafness (Including Hypoacusis), Tinnitus</td>
<td>Cataract</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation, Bradycardia</td>
<td>Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Arhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism ^</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism ^</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypotension, Hypertension, Ecchymosis ^</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common</td>
<td>Respiratory distress, Dyspnoea</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea, Epistaxis ^</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia</td>
<td>Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding) ^, Dry mouth, Stomatitis, Dysphagia</td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Common</td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Colitis, Caecitis</td>
<td>Hepatic failure ^</td>
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<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
<td>Common</td>
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<tr>
<td></td>
<td>Abnormal liver function tests</td>
<td>Cholestasis, Abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure ^</td>
<td>Hepatic failure ^</td>
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</table>
### System Organ Class / Preferred Term

<table>
<thead>
<tr>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
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</thead>
<tbody>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Rashies, Pruritus</td>
<td>Rashies</td>
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<tr>
<td>Common</td>
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<tr>
<td>Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
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<tr>
<td>Skin discoulouration, Photosensitivity reaction</td>
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<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Common</td>
</tr>
<tr>
<td>Common, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia</td>
<td>Muscular weakness, Bone pain</td>
</tr>
<tr>
<td>Common</td>
<td>Joint swelling</td>
</tr>
<tr>
<td>Uncommon</td>
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<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Very Common</td>
<td>Renal tubular necrosis</td>
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<tr>
<td>Renal failure (including acute)</td>
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<tr>
<td>Common</td>
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<tr>
<td>Haematuria^, Urinary retention, Urinary incontinence</td>
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<td>Uncommon</td>
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<tr>
<td>Acquired Fanconi syndrome</td>
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<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
<td>Erectile dysfunction</td>
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Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#  

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Grade 3−4 ADRs/Frequency</td>
</tr>
<tr>
<td></td>
<td>Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>very common pneumonia()³ &lt;br&gt; common infections (including opportunistic infections)⁶</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>very common pneumonia()³ &lt;br&gt; common infections (including opportunistic infections)⁶</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia(), Neutropenia(), Leucopenias</td>
<td>very common pneumonia()³ &lt;br&gt; common infections (including opportunistic infections)⁶</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td>common hyperglycaemia²⁷, decreased appetite⁷</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iron overload, Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Altered mood²⁷</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness, Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute myocardial infarction()³, Atrial fibrillation⁵, Cardiac failure⁵</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension, Haematoma</td>
<td>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism()³⁰</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common</td>
<td>common bronchitis⁷</td>
</tr>
<tr>
<td></td>
<td>Epistaxis()²⁷</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation</td>
<td>common diarrhoea²⁷, nausea, toothache⁷</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth, Dyspepsia</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
<td>common abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common</td>
<td>common rashes, pruritus⁷</td>
</tr>
<tr>
<td></td>
<td>Rashes, Dry Skin, Pruritus</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common</td>
<td>common back pain⁷</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td></td>
</tr>
</tbody>
</table>
System Organ Class / Preferred Term | All ADRs/Frequency | Grade 3−4 ADRs/Frequency
---|---|---
Renal and Urinary Disorders | Common Renal failure◊ | 
General Disorders and Administration Site Conditions | Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache) | Common Pyrexia
Injury, Poisoning and Procedural Complications | Common Fall | 

◊see section 4.8 description of selected adverse reactions

Adverse events reported as serious in myelodysplastic syndromes clinical trials

—Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event

# Algorithm applied for myelodysplastic syndromes:
- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td>Rare Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Not Known Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Not Known Pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>

152
### Description of selected adverse reactions

#### Teratogenicity

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

#### Neutropenia and thrombocytopenia

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone**

  The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

  The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

  The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

  The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

  The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**
SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**
*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

**Acute myeloid leukaemia**

- **Multiple myeloma**

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- **Myelodysplastic syndromes**

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality
compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

**Hepatic disorders**
The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Rhabdomyolysis**
Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

**Thyroid disorders**
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

**Gastrointestinal disorders**
Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in multiple myeloma patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

**Mechanism of action**
The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.
Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

Table 4: Summary of overall efficacy data

<table>
<thead>
<tr>
<th></th>
<th>Rd          (N = 541)</th>
<th>Rd18        (N = 540)</th>
<th>MPT         (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed PFS – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)b</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]; p-valuec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS2 – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS time, months (95% CI)b</td>
<td>42.9 (38.1, 47.4)</td>
<td>40.0 (36.2, 44.2)</td>
<td>35.0 (30.4, 37.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-valued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
150219_v31.0_Rev_EU_MM_MDS_PI_EN

<table>
<thead>
<tr>
<th></th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS time, months (95% CI)</td>
<td>58.9 (56.0, NE)</td>
<td>56.7 (50.1, NE)</td>
<td>48.5 (44.2, 52.0)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Rd vs MPT</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td>Rd vs Rd18</td>
</tr>
</tbody>
</table>

Follow-up (months)

| Median (min, max): all patients | 40.8 (0.0, 65.9) | 40.1 (0.4, 65.7) | 38.7 (0.0, 64.2) |

Myeloma response<sup>a</sup> n (%)

| CR | 81 (15.1) | 77 (14.2) | 51 (9.3) |
| VGPR | 152 (28.4) | 154 (28.5) | 103 (18.8) |
| PR | 169 (31.6) | 166 (30.7) | 187 (34.2) |
| Overall response: CR, VGPR, or PR | 402 (75.1) | 397 (73.4) | 341 (62.3) |

Duration of response – (months)<sup>b</sup>

| Median (95% CI) | 35.0 (27.9, 43.4) | 22.1 (20.3, 24.0) | 22.3 (20.2, 24.9) |

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio;

IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; Rd = lenalidomide; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

<sup>a</sup> The median is based on the Kaplan-Meier estimate.
<sup>b</sup> The 95% CI about the median.
<sup>c</sup> Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
<sup>d</sup> The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
<sup>e</sup> Exploratory endpoint (PFS2)
<sup>f</sup> The median is the univariate statistic without adjusting for censoring.
<sup>g</sup> Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category. Data cutoff date = 24 May 2013).
<sup>h</sup> data cut 24 May 2014

**Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplantation**

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+, 153 patients randomized to MP+p and 154 patients randomized to MPp+. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MP+p arms and 72 in the MPp+ arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5:
Table 5: Summary of overall efficacy data

<table>
<thead>
<tr>
<th></th>
<th>MPR+R (N = 152)</th>
<th>MPR+p (N = 153)</th>
<th>MPp +p (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator-assessed PFS – (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS time, months (95% CI)</td>
<td>27.4 (21.3, 35.0)</td>
<td>14.3 (13.2, 15.7)</td>
<td>13.1 (12.0, 14.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
<td>0.37 (0.27, 0.50); &lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>MPR+R vs MPR+p</td>
<td>0.47 (0.35, 0.65); &lt;0.001</td>
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</tr>
<tr>
<td>MPR+p vs MPp +p</td>
<td>0.78 (0.60, 1.01); 0.059</td>
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<tr>
<td><strong>PFS2 – (months)</strong>(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS time, months (95% CI)</td>
<td>39.7 (29.2, 48.4)</td>
<td>27.8 (23.1, 33.1)</td>
<td>28.8 (24.3, 33.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
<td>0.70 (0.54, 0.92); 0.009</td>
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<td></td>
</tr>
<tr>
<td>MPR+R vs MPR+p</td>
<td>0.77 (0.59, 1.02); 0.065</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+p vs MPp +p</td>
<td>0.92 (0.71, 1.19); 0.051</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) OS time, months (95% CI)</td>
<td>55.9 (49.1, 67.5)</td>
<td>51.9 (43.1, 60.6)</td>
<td>53.9 (47.3, 64.2)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR+R vs MPp+p</td>
<td>0.95 (0.70, 1.29); 0.736</td>
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<tr>
<td>MPR+R vs MPR+p</td>
<td>0.88 (0.65, 1.20); 0.43</td>
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</tr>
<tr>
<td>MPR+p vs MPp +p</td>
<td>1.07 (0.79, 1.45); 0.67</td>
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<tr>
<td><strong>Follow-up (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min, max): all patients</td>
<td>48.4 (0.8, 73.8)</td>
<td>46.3 (0.5, 71.9)</td>
<td>50.4 (0.5, 73.5)</td>
</tr>
<tr>
<td><strong>Investigator-assessed Myeloma response n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>30 (19.7)</td>
<td>17 (11.1)</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>PR</td>
<td>90 (59.2)</td>
<td>99 (64.7)</td>
<td>75 (48.7)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>24 (15.8)</td>
<td>31 (20.3)</td>
<td>63 (40.9)</td>
</tr>
<tr>
<td>Response Not Evaluable (NE)</td>
<td>8 (5.3)</td>
<td>4 (2.6)</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td><strong>Investigator-assessed Duration of response (CR+PR) – (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) (95% CI)</td>
<td>26.5 (19.4, 35.8)</td>
<td>12.4 (11.2, 13.9)</td>
<td>12.0 (9.4, 14.5)</td>
</tr>
</tbody>
</table>

\(^a\) The median is based on the Kaplan-Meier estimate
\(^b\) PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide / low dose dexamethasone tends to decrease.
Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).
Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/dex (N=351)</th>
<th>Hazard ratio [95% CI], p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to progression</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>48.1 [36.4, 62.1]</td>
<td>20.0 [16.1, 20.1]</td>
<td>0.393 [0.326, 0.473] p &lt; 0.001</td>
</tr>
<tr>
<td>Overall survival</td>
<td>164.3 [145.1, 192.6]</td>
<td>136.4 [113.1, 161.7]</td>
<td>0.833 [0.687, 1.009] p = 0.045</td>
</tr>
<tr>
<td>Overall response [n, %]</td>
<td>212 (60.1)</td>
<td>75 (21.4)</td>
<td>5.53 [3.97, 7.71], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete response [n, %]</td>
<td>58 (16.4)</td>
<td>11 (3.1)</td>
<td>6.08 [3.13, 11.80], p &lt; 0.001</td>
</tr>
</tbody>
</table>

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C<sub>max</sub>) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in C<sub>max</sub> in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

Distribution
In vitro (<sup>14</sup>C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).
Biotransformation and elimination

Results from human in vitro metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor in vivo, though it has no inhibitory effect at in vitro concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxylenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

Older people

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_max was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.
Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrioventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were >2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 21 capsules.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Revlimid 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 244.5 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Blue-green / Pale blue capsules, size 0, 21.7 mm, marked “REV 20 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
**Dose reduction steps**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Thrombocytopenia**

When platelets

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to &lt; 25 x 10^9/L</td>
<td>Stop lenalidomide dosing for remainder of cycle^a</td>
</tr>
<tr>
<td>Return to ≥ 50 x 10^9/L</td>
<td>Decrease by one dose level when dosing resumed at next cycle^a</td>
</tr>
</tbody>
</table>

^a If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

**Neutropenia**

When neutrophils

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide treatment at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide treatment at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide treatment at next lower dose level once daily</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered. If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

**Paediatric population**

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).
**Older people**

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

- Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

In clinical trials of newly diagnosed multiple myeloma in transplant non-eligible patients, lenalidomide combined therapy was less tolerated in the patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years. (see Section 4.4).

**Patients with renal impairment**

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis).

- Multiple myeloma

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment (30 ≤ CLcr &lt; 50 mL/min)</td>
<td>10 mg once daily¹</td>
</tr>
<tr>
<td>Severe renal impairment (CLcr &lt; 30 mL/min, not requiring dialysis)</td>
<td>7.5 mg once daily² 15 mg every other day</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD) (CLcr &lt; 30 mL/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

¹ The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

² In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

**Patients with hepatic impairment**

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

**Method of administration**

Oral use.
Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
150219_v31.0_Rev_EU_MM_MDS_PI_EN

- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

**Contraception**

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:
- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

**Pregnancy testing**

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

**Prior to starting treatment**

A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.
Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy,
should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

**Neutropenia and thrombocytopenia**

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8. Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPP+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medications that increase susceptibility to bleeding (see section 4.8 Haemorrhagic disorders).
Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Renal impairment
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

Tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Second primary malignancies
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).
A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

**Hepatic disorders**

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min (see section 4.2 and 4.8).

**Cataract**

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

### 4.5 Interaction with other medicinal products and other forms of interaction
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested, did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%–28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

**Statins**

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

**Dexamethasone**

Co-administration of single or multiple doses of dexamethasone (40 mg/day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/day).

**Interactions with P-glycoprotein (P-gp) inhibitors**

*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

### 4.6 Fertility, pregnancy and lactation

**Women of childbearing potential / Contraception in males and females**

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose...
interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

**Pregnancy**
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

**Breast-feeding**
It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

**Fertility**
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

**4.7 Effects on ability to drive and use machines**

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

**4.8 Undesirable effects**

**Summary of the safety profile**

**Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone**

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

**Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

**Multiple myeloma with at least one prior therapy**
In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism).
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
</table>

175
<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis, Sinusitis</td>
<td></td>
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<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma, Squamous skin cancer^*</td>
<td>Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Neutropenia^, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenia</td>
<td>T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
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<tr>
<td></td>
<td>Febrile neutropenia, Pancytopenia</td>
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<tr>
<td></td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
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<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity^</td>
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<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Common</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
<td></td>
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<tr>
<td></td>
<td>Common</td>
<td></td>
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<tr>
<td></td>
<td>Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
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<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Very Common</td>
<td></td>
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<tr>
<td></td>
<td>Depression, Insomnia</td>
<td></td>
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<tr>
<td></td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Loss of libido</td>
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<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia,</td>
<td></td>
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<tr>
<td></td>
<td>Headache</td>
<td></td>
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<td></td>
<td>Common</td>
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<tr>
<td></td>
<td>Ataxia, Balance impaired</td>
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<tr>
<td><strong>Eye Disorders</strong></td>
<td>Very Common</td>
<td></td>
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<tr>
<td></td>
<td>Cataracts, Blurred vision</td>
<td></td>
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<tr>
<td></td>
<td>Common</td>
<td></td>
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<tr>
<td></td>
<td>Reduced visual acuity</td>
<td></td>
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<td></td>
<td>Common</td>
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<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3−4 ADRs/Frequency</td>
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<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td>Common Deafness (Including Hypoacusis), Tinnitus</td>
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<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common Atrial fibrillation, Bradycardia&lt;br&gt;Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td>Common Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^&lt;br&gt;Common Hypotension, Hypertension, Ecchymosis^&lt;br&gt;Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^&lt;br&gt;Common Vasculitis&lt;br&gt;Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Dyspnoea, Epistaxis^&lt;br&gt;Common Respiratory distress, Dyspnoea</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia&lt;br&gt;Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^&lt;br&gt;Common Colitis, Caecitis</td>
<td>Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common Abnormal liver function tests&lt;br&gt;Uncommon Hepatic failure^&lt;br&gt;Common Cholestasis, Abnormal liver function tests&lt;br&gt;Uncommon Hepatic failure^&lt;br&gt;Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common Rashes, Pruritus&lt;br&gt;Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema&lt;br&gt;Uncommon Skin discoloration, Photosensitivity reaction</td>
<td>Common Rashes</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia&lt;br&gt;Common Muscular weakness, Joint swelling, Myalgia</td>
<td>Common Muscular weakness, Bone pain&lt;br&gt;Uncommon Joint swelling</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Very Common Renal failure (including acute)</td>
<td>Uncommon Renal tubular necrosis</td>
</tr>
<tr>
<td></td>
<td>Common Haematuria^, Urinary retention, Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon Acquired Fanconi syndrome</td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Common Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy</td>
<td>Common Fatigue, Pyrexia, Asthenia</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common C-reactive protein increased</td>
<td></td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Common Fall, Contusion^</td>
<td></td>
</tr>
</tbody>
</table>

^See section 4.8 description of selected adverse reactions
* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.
Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3−4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Very Common Pneumonia◊</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common Thrombocytopenia◊, Neutropenia◊, Leucopenias</td>
<td>Very Common Thrombocytopenia◊, Neutropenia◊, Leucopenias</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common Decreased appetite, Iron overload, Weight decreased</td>
<td>Common Hyperglycaemia◊, Decreased appetite</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td>Common Altered mood◊</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common Dizziness, Headache, Paraesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td>Common Acute myocardial infarction◊, Atrial fibrillation◊, Cardiac failure◊</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common Hypertension, Haematoma</td>
<td>Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism◊</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Epistaxis◊</td>
<td>Common Bronchitis</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation</td>
<td>Common Diarrhoea◊, Nausea, Toothache</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common Abnormal liver function tests</td>
<td>Common Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common Rashes, Dry Skin, Pruritus</td>
<td>Common Rashes, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td>Common Back pain◊</td>
</tr>
</tbody>
</table>
### System Organ Class / Preferred Term

#### Renal and Urinary Disorders
- **All ADRs/Frequency**
  - Common Renal failure  
- **Grade 3−4 ADRs/Frequency**
  - Common Renal failure

#### General Disorders and Administration Site Conditions
- **All ADRs/Frequency**
  - Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)
- **Grade 3−4 ADRs/Frequency**
  - Common Pyrexia

#### Injury, Poisoning and Procedural Complications
- **All ADRs/Frequency**
  - Common Fall
- **Grade 3−4 ADRs/Frequency**
  - Common Fall

---

*see section 4.8 description of selected adverse reactions

◊ Adverse events reported as serious in myelodysplastic syndromes clinical trials

~ Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event

# Algorithm applied for myelodysplastic syndromes:
- **Myelodysplastic syndromes Phase III study**
  - All treatment-emergent adverse events with $\geq 5\%$ of subjects in lenalidomide at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo

- **Myelodysplastic syndromes Phase II study**
  - All treatment-emergent adverse events with $\geq 5\%$ of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

- **Algorithm applied for inclusion in the SmPC**: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

### Tabulated summary of post-marketing adverse reactions

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

#### Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3−4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)</td>
<td></td>
<td>Rare Tumour lysis syndrome</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td>Not Known Interstitial pneumonitis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td>Not Known Pancreatitis</td>
</tr>
</tbody>
</table>
### Description of selected adverse reactions

**Teratogenicity**  
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

**Neutropenia and thrombocytopenia**

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone**

  The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

  The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- **Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone**

  The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

  The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- **Multiple myeloma with at least one prior therapy**

  The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

---

*see section 4.8 description of selected adverse reactions*
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**

The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma and to a lesser extent in patients treated with melphalan and prednisone (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**

*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

**Acute myeloid leukaemia**

- **Multiple myeloma**

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed, in clinical trials of newly diagnosed multiple myeloma patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- **Myelodysplastic syndromes**

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. The estimated 2-year
The cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

**Hepatic disorders**

The following post marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Rhabdomyolysis**

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

**Thyroid disorders**

Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

**Gastrointestinal disorders**

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in multiple myeloma patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

**Mechanism of action**

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation.
resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

Table 4: Summary of overall efficacy data

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>Rd (N = 541)</th>
<th>Rd18 (N = 540)</th>
<th>MPT (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS time, months (95% CI)b</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]; p-valuec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFS2 – (months)</th>
<th>Median PFS time, months (95% CI)b</th>
<th>42.9 (38.1, 47.4)</th>
<th>40.0 (36.2, 44.2)</th>
<th>35.0 (30.4, 37.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR [95% CI]; p-valuec</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival (months)</th>
<th>Median OS time, months (95% CI)b</th>
<th>58.9 (56.0, NE)</th>
<th>56.7 (50.1, NE)</th>
<th>48.5 (44.2, 52.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR [95% CI]; p-valued</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td></td>
</tr>
</tbody>
</table>
Surviving subjects was 62.4 months, the results of the study are presented in Table 5.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

Patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were eligible for transplantation.
MPR+R vs MPp+p 
(N = 152) 
0.78 (0.60, 1.01); <0.001

MPR+R vs MPp+p 
(N = 152) 
0.84 (0.60, 1.01); <0.001

MPR+p vs MPp+p 
(N = 154) 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.47 (0.35, 0.65); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.47 (0.35, 0.65); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.37 (0.27, 0.50); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.47 (0.35, 0.65); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.37 (0.27, 0.50); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.47 (0.35, 0.65); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.37 (0.27, 0.50); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

MPR+R vs MPp+p 
0.47 (0.35, 0.65); <0.001

MPR+p vs MPp+p 
0.78 (0.60, 1.01); 0.059

PFS2 (months) 
Median PFS time, months (95% CI) 
39.7 (29.2, 48.4) 
27.8 (23.1, 33.1) 
28.8 (24.3, 33.8)

HR [95% CI]; p-value 
MPR+R vs MPp+p 
0.70 (0.54, 0.92); 0.009

MPR+R vs MPp+p 
0.77 (0.59, 1.02); 0.065

MPR+p vs MPp+p 
0.92 (0.71, 1.19); 0.051

Overall survival (months) 
Median OS time, months (95% CI) 
55.9 (49.1, 67.5) 
51.9 (43.1, 60.6) 
53.9 (47.3, 64.2)

HR [95% CI]; p-value 
MPR+R vs MPp+p 
0.70 (0.54, 0.92); 0.009

MPR+R vs MPp+p 
0.77 (0.59, 1.02); 0.065

MPR+p vs MPp+p 
0.92 (0.71, 1.19); 0.051

Follow-up (months) 
Median (min, max): all patients 
48.4 (0.8, 73.8) 
46.3 (0.5, 71.9) 
50.4 (0.5, 73.3)

Investigator-assessed Myeloma response n (%) 
CR 
30 (19.7) 
17 (11.1) 
9 (5.8)

PR 
90 (59.2) 
99 (64.7) 
75 (48.7)

Stable Disease (SD) 
24 (15.8) 
31 (20.3) 
63 (40.9)

Response Not Evaluable (NE) 
8 (5.3) 
4 (2.6) 
7 (4.5)

Investigator-assessed Duration of response (CR+PR) – (months) 
Median* (95% CI) 
26.5 (19.4, 35.8) 
12.4 (11.2, 13.9) 
12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

The median is based on the Kaplan-Meier estimate

PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients

Supportive newly diagnosed multiple myeloma studies
An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm.

Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide / low dose dexamethasone tends to decrease.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).
5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C\text{max}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R-enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in C\text{max} in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

Distribution

\textit{In vitro} (14C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

Biotransformation and elimination

Results from human \textit{in vitro} metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. \textit{In vitro} studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

\textit{In vitro} studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor \textit{in vivo}, though it has no inhibitory effect at \textit{in vitro} concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.
At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

**Older people**

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

**Renal impairment**

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The $C_{\text{max}}$ was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

**Hepatic impairment**

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

**Other intrinsic factors**

Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

### 5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 to up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of
white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

*In vitro* (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Capsule contents**
- Lactose, anhydrous
- Cellulose, microcrystalline
- Croscarmellose sodium
- Magnesium stearate

**Capsule shell**
- Gelatin
- Titanium dioxide (E171)
- Indigo carmine (E132)
- Yellow iron oxide (E172)

**Printing ink**
- Shellac
- Propylene glycol
- Black iron oxide (E172)
- Potassium hydroxide

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 21 capsules.

6.6 **Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
1. **NAME OF THE MEDICINAL PRODUCT**

Revlimid 25 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 25 mg of lenalidomide.

Excipient(s) with known effect:
Each capsule contains 200 mg of lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.
White capsules, size 0, 21.7 mm, marked “REV 25 mg”.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

4.2 **Posology and method of administration**

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

**Posology**

**Newly diagnosed multiple myeloma**

*Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant*

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.
Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Dose reduction steps</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
</table>
  | Fall to < 25 x 10^9/L | Stop lenalidomide dosing for remainder of cycle
  | Return to ≥ 50 x 10^9/L | Decrease by one dose level when dosing resumed at next cycle

  *If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below &lt; 0.5 x 10^9/L</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to ≥ 0.5 x 10^9/L</td>
<td>Resume lenalidomide at next lower dose level once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.
If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

**Multiple myeloma with at least one prior therapy**

**Recommended dose**
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.
Recommended dose adjustments during treatment and restart of treatment:
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- **Dose reduction steps**

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>25 mg</th>
</tr>
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<tbody>
<tr>
<td>Dose level -1</td>
<td>15 mg</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>10 mg</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

- **Thrombocytopenia**

<table>
<thead>
<tr>
<th>When platelets</th>
<th>Recommended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fall to $&lt; 30 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 30 \times 10^9/L$</td>
<td>Resume lenalidomide at Dose level -1</td>
</tr>
<tr>
<td>For each subsequent drop below $30 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 30 \times 10^9/L$</td>
<td>Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

- **Neutropenia**

<table>
<thead>
<tr>
<th>When neutrophils</th>
<th>Recommended course</th>
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</thead>
<tbody>
<tr>
<td>First fall to $&lt; 0.5 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$ when neutropenia is the only observed toxicity</td>
<td>Resume lenalidomide at Starting dose once daily</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed</td>
<td>Resume lenalidomide at Dose level -1 once daily</td>
</tr>
<tr>
<td>For each subsequent drop below $&lt; 0.5 \times 10^9/L$</td>
<td>Interrupt lenalidomide treatment</td>
</tr>
<tr>
<td>Return to $\geq 0.5 \times 10^9/L$</td>
<td>Resume lenalidomide at next lower dose level (Dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the use of growth factors in patient management should be considered.

**All patients**
For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to $\leq$ grade 2 depending on the physician’s discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

**Special populations**

**Paediatric population**
Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

**Older people**
Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).
In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

- Newly diagnosed multiple myeloma

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in the patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years. (see Section 4.4).

- Multiple myeloma with at least one prior therapy

The percentage of patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

**Patients with renal impairment**

Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (Clcr < 30 ml/min, requiring dialysis).

- **Multiple myeloma**

<table>
<thead>
<tr>
<th>Renal function (CLcr)</th>
<th>Dose adjustment (Days 1 to 21 of repeated 28-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate renal impairment</td>
<td></td>
</tr>
<tr>
<td>(30 ≤ Clcr &lt; 50 ml/min)</td>
<td>10 mg once daily†</td>
</tr>
<tr>
<td>Severe renal impairment (Clcr &lt; 30 ml/min, not requiring dialysis)</td>
<td>7.5 mg once daily‡ 15 mg every other day</td>
</tr>
<tr>
<td>End Stage Renal Disease (ESRD)</td>
<td></td>
</tr>
<tr>
<td>(Clcr &lt; 30 ml/min, requiring dialysis)</td>
<td>5 mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
</tr>
</tbody>
</table>

† The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.
‡ In countries where the 7.5 mg capsule is available.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

**Patients with hepatic impairment**

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.
Method of administration
Oral use.

Revlimid capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:
- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.
*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhoea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
• Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
• Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
• Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:
• The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
• The patient has acknowledged the aforementioned conditions.

Contraception
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:
• Implant
• Levonorgestrel-releasing intrauterine system (IUS)
• Medroxyprogesterone acetate depot
• Tubal sterilisation
• Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
• Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective
contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes. See sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking,
hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

**Neutropenia and thrombocytopenia**

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 (treatment for 18 four-week cycles) compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8. Patients should be advised to promptly report febrile episodes and dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients; see section 4.8).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in...
patients receiving concomitant medicinal products that increase susceptibility to bleeding (see section 4.8 Haemorrhagic disorders).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

**Infection with or without neutropenia**

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

**Renal impairment**

Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (see section 4.2).

**Thyroid disorders**

Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

**Peripheral neuropathy**

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

**Tumour lysis syndrome**

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction.
depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

*Lactose intolerance*
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

*Unused capsules*
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

*Second primary malignancies*
An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin’s lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

*Hepatic disorders*
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.
Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

**Newly diagnosed multiple myeloma patients**

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min (see section 4.2 and 4.8).

**Cataract**

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

### 4.5 Interaction with other medicinal products and other forms of interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see sections 4.4 and 4.8).

**Oral contraceptives**

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

**Warfarin**

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

**Digoxin**

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

**Statins**

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

**Dexamethasone**

Co-administration of single or multiple doses of dexamethasone (40 mg/ day) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/ day).
Interactions with P-glycoprotein (P-gp) inhibitors

*In vitro*, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6  Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

Fertility

A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7  Effects on ability to drive and use machines

Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8  Undesirable effects

Summary of the safety profile

*Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone*

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)
The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+ p than MPP+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma with at least one prior therapy

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia

The most commonly observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

Tabulated summary for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon.
(≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.
Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis</td>
<td>Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis, Sinusitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin**</td>
<td></td>
</tr>
<tr>
<td>Squamous skin cancer^*</td>
<td>Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Neutropenia^, Thrombocytopenia ^, Anaemia, Haemorrhagic disorder ^, Leucopenias</td>
<td>Neutropenia^, Thrombocytopenia ^, Anaemia, Leucopenias</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia, Pancytopenia</td>
<td>Febrile neutropenia ^, Pancytopenia, Haemolytic anaemia</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td>Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Hypersensitivity^</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyperonatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased</td>
<td>Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyperonatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td>Hypomagnesaemia, Hyperuricaemia, Dehydration</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Depression, Insomnia</td>
<td>Depression, Insomnia</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Loss of libido</td>
<td>Loss of libido</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache</td>
<td>Cerebrovascular accident, Dizziness, Syncope</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Ataxia, Balance impaired</td>
<td>Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Cataracts, Blurred vision</td>
<td>Cataract</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Reduced visual acuity</td>
<td>Blindness</td>
<td></td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3–4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td>Common Deafness (Including Hypoacusis), Tinnitus</td>
<td>Common Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common Atrial fibrillation, Bradycardia, Bradycardia</td>
<td>Common Myocardial infarction (including acute) ^, Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism ^</td>
<td>Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism ^</td>
</tr>
<tr>
<td></td>
<td>Common Hypotension, Hypertension, Ecchymosis ^</td>
<td>Common Vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncommon Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Dyspnoea, Epistaxis ^</td>
<td>Common Respiratory distress, Dyspnoea</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia</td>
<td>Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting</td>
</tr>
<tr>
<td></td>
<td>Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding ^), Dry mouth, Stomatitis, Dysphagia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon Colitis, Caecitis</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common Abnormal liver function tests</td>
<td>Common Cholestasis, Abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>Uncommon Hepatic failure ^</td>
<td>Uncommon Hepatic failure ^</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Common Rashes</td>
<td>Common Rashes</td>
</tr>
<tr>
<td></td>
<td>Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon Skin discoloration, Photosensitivity reaction</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia</td>
<td>Common Muscular weakness, Bone pain</td>
</tr>
<tr>
<td></td>
<td>Common Muscular weakness, Joint swelling, Myalgia</td>
<td>Uncommon Joint swelling</td>
</tr>
<tr>
<td>System Organ Class / Preferred Term</td>
<td>All ADRs/Frequency</td>
<td>Grade 3−4 ADRs/Frequency</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Very Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Renal failure (including acute)</td>
<td>Renal tubular necrosis</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haematuria*, Urinary retention, Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acquired Fanconi syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors)</td>
<td>Fatigue, Pyrexia, Asthenia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest pain, Lethargy</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-reactive protein increased</td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fall, Contusion^</td>
<td></td>
</tr>
</tbody>
</table>

*See section 4.8 description of selected adverse reactions

*Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

**Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary from monotherapy

The adverse reactions observed in patients treated for myelodysplastic syndromes are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes.

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.
Table 2: ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Very Common Bacterial, viral and fungal infections (including opportunistic infections)</td>
<td>Very Common Pneumonia(^\circ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common Bacterial, viral and fungal infections (including opportunistic infections)(^\circ)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Very Common Thrombocytopenia(^\wedge), Neutropenia(^\wedge), Leucopenias</td>
<td>Very Common Thrombocytopenia(^\wedge), Neutropenia(^\wedge), Leucopenias(^\circ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common Febrile Neutropenia(^\wedge)</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very Common Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Very Common Decreased appetite</td>
<td>Common Hyperglycaemia(^\circ), Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Common Iron overload, Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td>Common Altered mood(^\wedge)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very Common Dizziness, Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common Paraesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td>Common Acute myocardial infarction(^\wedge), Atrial fibrillation(^\circ), Cardiac failure(^\circ)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common Hypertension, Haematoma</td>
<td>Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism(^\circ)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Very Common Epistaxis(^\wedge)</td>
<td>Common Bronchitis</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Very Common Diarrhoea, Abdominal pain (including upper), Nausea, Vomiting, Constipation</td>
<td>Common Diarrhoea(^\wedge), Nausea, Toothache</td>
</tr>
<tr>
<td></td>
<td>Common Dry mouth, Dyspepsia</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td>Common Abnormal liver function tests</td>
<td>Common Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Very Common Rashes, Dry Skin, Pruritus</td>
<td>Common Rashes, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Very Common Muscle spasms, Musculoskeletal pain (including back pain and pain in extremity), Arthralgia, Myalgia</td>
<td>Common Back pain(^\circ)</td>
</tr>
</tbody>
</table>
**System Organ Class / Preferred Term** | **All ADRs/Frequency** | **Grade 3–4 ADRs/Frequency**
--- | --- | ---
Renal and Urinary Disorders | Common Renal failure\(^o\) | 
General Disorders and Administration Site Conditions | Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache) | Common Pyrexia
Injury, Poisoning and Procedural Complications | Common Fall | 

\(^{o}\) Adverse events reported as serious in myelodysplastic syndromes clinical trials
\(^{\circ}\) Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event
# Algorithm applied for myelodysplastic syndromes:
- Myelodysplastic syndromes Phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

**Tabulated summary of post-marketing adverse reactions**

In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

**Table 3: ADRs reported in in post-marketing use in patients with multiple myeloma treated with lenalidomide**

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>All ADRs/Frequency</th>
<th>Grade 3–4 ADRs/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</td>
<td></td>
<td>Rare Tumour lysis syndrome</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Common Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Not Known Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Not Known Pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>
System Organ Class / Preferred Term | All ADRs/Frequency | Grade 3–4 ADRs/Frequency
--- | --- | ---
Hepatobiliary Disorders | Not Known | Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^ | Not Known | Acute hepatic failure^, Hepatitis toxic^ |
Skin and Subcutaneous Tissue Disorders | Uncommon | Angioedema | Rare | Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ | Not Known | Leukocytoclastic vasculitis

^see section 4.8 description of selected adverse reactions

Description of selected adverse reactions

**Teratogenicity**
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

**Neutropenia and thrombocytopenia**

- Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1 in Rd and Rd18 compared to 11% in MPT).

- Newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in MPR+R/MPR+p compared with 7.8% in MPp+p). There was a higher incidence of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

- Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

- **Myelodysplastic syndromes**

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

**Venous thromboembolism**

The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma, and to a lesser extent in patients treated with melphalan and prednisone (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

**Myocardial infarction**

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

**Haemorrhagic disorders**

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

**Allergic reactions**

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

**Severe skin reactions**

SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**Second primary malignancies**

*In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

**Acute myeloid leukaemia**

- **Multiple myeloma**

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4). This increase was not observed, in clinical trials of newly diagnosed multiple myeloma patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- **Myelodysplastic syndromes**

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. The estimated 2-year
cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5% in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

**Hepatic disorders**

The following post marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Rhabdomyolysis**

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

**Thyroid disorders**

Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

**Gastrointestinal disorders**

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 **Overdose**

There is no specific experience in the management of lenalidomide overdose in multiple myeloma patients, although in dose-ranging studies some patients were exposed to up to 150 mg, and in single-dose studies, some patients were exposed to up to 400 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

**Mechanism of action**

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation
resulting in cytoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

<table>
<thead>
<tr>
<th></th>
<th>Rd</th>
<th>Rd18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 541)</td>
<td>(N = 540)</td>
<td>(N = 542)</td>
</tr>
<tr>
<td>Investigator-assessed PFS – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS time, months (95% CI)(^b)</td>
<td>26.0 (20.7, 29.7)</td>
<td>21.0 (19.7, 22.4)</td>
<td>21.9 (19.8, 23.9)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.69 (0.59, 0.80); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.71 (0.61, 0.83); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.99 (0.86, 1.14); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS2(^e) – (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) PFS2 time, months (95% CI)(^b)</td>
<td>42.9 (38.1, 47.4)</td>
<td>40.0 (36.2, 44.2)</td>
<td>35.0 (30.4, 37.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.74 (0.63, 0.86); &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.92 (0.78, 1.08); 0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd18 vs MPT</td>
<td>0.80 (0.69, 0.93); 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(^a) OS time, months (95% CI)(^b)</td>
<td>58.9 (56.0, NE)</td>
<td>56.7 (50.1, NE)</td>
<td>48.5 (44.2, 52.0)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs MPT</td>
<td>0.75 (0.62, 0.90); 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd vs Rd18</td>
<td>0.91 (0.75, 1.09); 0.305</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 5:

Table 5: Summary of overall efficacy data

<table>
<thead>
<tr>
<th>Investigator-assessed PFS – (months)</th>
<th>MPR+R (N = 152)</th>
<th>MPR+p (N = 153)</th>
<th>MP+ (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS time, months (95% CI)</td>
<td>27.4 (21.3, 35.0)</td>
<td>14.3 (13.2, 15.7)</td>
<td>13.1 (12.0, 14.8)</td>
</tr>
<tr>
<td>HR [95% CI]; p-value</td>
<td>0.37 (0.27, 0.50); &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of lenalidomide / low dose dexamethasone tends to decrease.

Multiple myeloma with at least one prior therapy

The efficacy and safety of lenalidomide were evaluated in two Phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6%
were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group. Both patient populations presented a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 6 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone.

The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 6: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/dex (N=351)</th>
<th>Hazard ratio [95% CI], p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression</td>
<td>60.1 [44.3, 73.1]</td>
<td>20.1 [17.7, 20.3]</td>
<td>0.350 [0.287, 0.426], p &lt; 0.001</td>
</tr>
</tbody>
</table>

Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)
### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

#### 5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

**Absorption**

Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration ($C_{\text{max}}$) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in $C_{\text{max}}$ in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar between MM and MDS patients.

**Distribution**

*In vitro* ($^{14}$C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

**Biotransformation and elimination**

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6,
Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

It is unknown whether lenalidomide is a human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 inhibitor in vivo, though it has no inhibitory effect at in vitro concentrations up to 20 µM.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxylenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

Older people
No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment
The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The Cmax was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment
Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (33-135 kg), gender, race and type of haematological malignancy (MM or MDS) do not have a clinically relevant effect on lenalidomide clearance in adult patients.
5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and in vivo (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Cellulose, microcrystalline
Crocarmellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.
6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Pack size of 21 capsules.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORITY

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/07/391/004

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 14 June 2007
Date of latest renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

19/02/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.
ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
United Kingdom

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING THE SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports
  The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)
  The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Additional risk minimisation measures
  1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
     - Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
Prior to prescribing (and where appropriate, and in agreement with the National Competent Authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:

- Educational Health Care Professional’s kit
- Educational brochures for Patients
- Patient cards
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

4. The MAH should agree on the implementation of the patient card system in each Member State.

5. The MAH should also agree with each Member State:
   - The details of the implementation of the MDS Post-Authorisation Safety Study (MDS PASS)
   - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

**Direct Healthcare Professional Communications**

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
  - Distribution of the product
  - To ensure that all appropriate measures have been performed prior to Revlimid being dispensed

**The Educational Healthcare Professional’s Kit**

The Educational Health Care Professional’s Kit shall contain the following elements:

- Brief background on lenalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the results of study CC-5013-TOX-004
- Obligations of the health care professional in relation to the prescribing of Revlimid
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Revlimid
  - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
  - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
  - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
  - Use in patients with hepatic and/or renal impairment
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Revlimid to be dispensed
  - Description of risk of hypothyroidism
 Explanation of unknown risk of neuropathy with long term use
 o Description of the risk of progression to AML in MDS patients including incidence rates from clinical trials

 • **Description of the PPP and categorisation of patients based on sex and childbearing potential**
   o Algorithm for implementation of PPP
   o Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure

 • **Safety advice for women of childbearing potential**
   o The need to avoid foetal exposure
   o Description of the PPP
   o Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
   o Pregnancy test regime
     ▪ Advice on suitable tests
     ▪ Before commencing treatment
     ▪ During treatment based on method of contraception
     ▪ After finishing treatment
   o Need to stop Revlimid immediately upon suspicion of pregnancy
   o Need to tell treating doctor immediately upon suspicion of pregnancy

 • **Safety advice for men**
   o The need to avoid foetal exposure
   o The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had a vasectomy)
     ▪ During Revlimid treatment
     ▪ For one week following final dose.
   o That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately

 • **Requirements in the event of pregnancy**
   o Instructions to stop Revlimid immediately upon suspicion of pregnancy
   o Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
   o Local contact details for reporting of any suspected pregnancy
   o Pregnancy reporting form

 • **Check list for physicians** ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status

 • **Details on the MDS PASS** emphasizing that prior to prescribing Revlimid, the healthcare professionals should enroll MDS patients into the PASS.

 • Adverse event reporting forms

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**Educational Brochures for patients**

The Educational brochures for patients should be of 3 types:

 • Brochure for women patients of childbearing potential and their partners
 • Brochure for women patients who are not of childbearing potential
 • Brochure for male patients

All patient brochures should contain the following elements:

 • That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
 • That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
 • That Revlimid may cause venous and arterial thromboembolism
 • Description of the patient card and its necessity
 • Disposal of unwanted medicine
 • National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
 • That the patient should not give Revlimid to any other person
 • That the patient should not donate blood
• That the patient should tell their doctor about any adverse events
• That a study is being conducted to collect information regarding the safety of the drug and to monitor its appropriate use; and that MDS patients should be included in the study prior to the start of the treatment with Revlimid

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential
• The need to avoid foetal exposure
• Description of the PPP
• Need for adequate contraception and definition of adequate contraception
• Pregnancy test regime
  o Before commencing treatment
  o During treatment, every 4 weeks except in case of confirmed tubal sterilisation
  o After finishing treatment
• The need to stop Revlimid immediately upon suspicion of pregnancy
• The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients
• The need to avoid foetal exposure
• The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had vasectomy)
  o During Revlimid treatment
  o For one week following final dose
• That if his partner becomes pregnant he should inform his treating doctor immediately

Patient Card

The patient card shall contain the following elements:
• Verification that appropriate counselling has taken place
• Documentation of childbearing status potential
• Pregnancy test dates and results

• Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use.</td>
<td>Annual safety updates with PSURs</td>
</tr>
<tr>
<td>A post-authorisation non-interventional, safety study of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide to gather safety data on the use of lenalidomide in NDMM patients.</td>
<td>Annual safety updates with PSURs</td>
</tr>
</tbody>
</table>
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 2.5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2.5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 or 21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.
Lenalidomide is expected to be harmful to an unborn child.

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/005
EU/1/07/391/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 2.5 mg
## MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

### BLISTERS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td></td>
<td>Revlimid 2.5 mg hard capsules</td>
</tr>
<tr>
<td></td>
<td>lenalidomide</td>
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<td><strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
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<td></td>
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<td>4</td>
<td><strong>BATCH NUMBER</strong></td>
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<td></td>
<td>Lot</td>
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<tr>
<td>5</td>
<td><strong>OTHER</strong></td>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 or 21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
UB11 1DB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/001  
EU/1/07/391/008

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 5 mg
### Minimum Particulars to Appear on Blisters or Strips

#### Blisters

1. **Name of the Medicinal Product**
   - Revlimid 5 mg hard capsules
   - lenalidomide

2. **Name of the Marketing Authorisation Holder**
   - Celgene Europe Limited

3. **Expiry Date**
   - EXP

4. **Batch Number**
   - Lot

5. **Other**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 7.5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORITY HOLDING**

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. **MARKETING AUTHORIZATION NUMBER(S)**

EU/1/07/391/006

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 7.5 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Revlimid 10 mg hard capsules
   lenalidomide

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each capsule contains 10 mg lenalidomide.

3. **LIST OF EXCIPIENTS**
   
   It contains lactose.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   21 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   For oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**
   
   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
   
   Use only as directed by your doctor.
   
   Lenalidomide is expected to be harmful to an unborn child.

8. **EXPIRY DATE**
   
   EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
UB11 1DB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/002

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 10 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

#### 1. NAME OF THE MEDICINAL PRODUCT

Revlimid 10 mg hard capsules
lenalidomide

#### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

#### 3. EXPIRY DATE

EXP

#### 4. BATCH NUMBER

Lot

#### 5. OTHER
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

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<th>Details</th>
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<td>Revlimid 15 mg hard capsules lenalidomide</td>
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<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
<td>Each capsule contains 15 mg lenalidomide.</td>
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<td><strong>3. LIST OF EXCIPIENTS</strong></td>
<td>It contains lactose.</td>
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<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
<td>21 hard capsules</td>
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<tr>
<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td>For oral use. Read the package leaflet before use.</td>
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<tr>
<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></td>
<td>Keep out of the sight and reach of children.</td>
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<tr>
<td><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></td>
<td>Use only as directed by your doctor. Lenalidomide is expected to be harmful to an unborn child.</td>
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<td><strong>8. EXPIRY DATE</strong></td>
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9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
UB11 1DB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/003

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 15 mg
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<tr>
<td>lenalidomide</td>
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</tr>
<tr>
<td>Celgene Europe Limited</td>
</tr>
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<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>EXP</td>
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<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
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</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 20 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 20 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.
Lenalidomide is expected to be harmful to an unborn child.

8. Expiry date

EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
UB11 1DB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/009

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 20 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTERS**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Revlimid 20 mg hard capsules
   lenalidomide

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   Celgene Europe Limited

3. **EXPIRY DATE**
   
   EXP

4. **BATCH NUMBER**
   
   Lot

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 25 mg hard capsules lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 25 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Unused medicinal product should be returned to the pharmacist.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
UB11 1DB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/391/004

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Revlimid 25 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 25 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

Revlimid 2.5 mg hard capsules
Revlimid 5 mg hard capsules
Revlimid 7.5 mg hard capsules
Revlimid 10 mg hard capsules
Revlimid 15 mg hard capsules
Revlimid 20 mg hard capsules
Revlimid 25 mg hard capsules

lenalidomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.**
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Revlimid is and what it is used for
2. What you need to know before you take Revlimid
3. How to take Revlimid
4. Possible side effects
5. How to store Revlimid
6. Content of the pack and other information

1. What Revlimid is and what it is used for

What Revlimid is
Revlimid contains the active substance ‘lenalidomide’. This medicine belongs to a group of medicines which affect how your immune system works.

Revlimid is used in adults for:
1. Multiple myeloma
2. Myelodysplastic syndromes

Multiple Myeloma and Revlimid

Multiple myeloma is a type of cancer which affects a certain type of white blood cell, called the plasma cell. These cells collect in the bone marrow and divide out of control. This can damage the bones and kidneys.

Multiple myeloma generally cannot be cured. However, the signs and symptoms can be greatly reduced or disappear for a period of time. This is called a ‘response’.

When used to treat multiple myeloma, Revlimid is used in combination with other medicines.

**Revlimid in patients newly diagnosed with multiple myeloma**
Revlimid is only used in newly diagnosed patients when you are unable to be treated with a bone marrow transplant.

If you are aged 75 years or older or have moderate to severe kidney problems - your doctor will check you carefully before starting treatment.
In newly diagnosed patients there are two types of treatment:
- Revlimid together with an anti-inflammatory medicine called ‘dexamethasone’.
Revlimid together with a chemotherapy medicine called ‘melphalan’ and an immunosuppressant medicine called ‘prednisone’. You will take these other medicines at the start of treatment and then continue to take Revlimid on its own.

**Revlimid in patients who have had at least one other type of treatment before**
- Revlimid is taken together with an anti-inflammatory medicine called ‘dexamethasone’.

Revlimid can stop the signs and symptoms of multiple myeloma getting worse. It has also been shown to delay multiple myeloma from coming back following treatment.

**Myelodysplastic syndromes and Revlimid**
Myelodysplastic syndromes (MDS) are a collection of many different blood and bone marrow diseases. The blood cells become abnormal and do not function properly. Patients can experience a variety of signs and symptoms including a low red blood cell count (anaemia), the need for a blood transfusion, and a risk of infection.

Revlimid is used alone to treat adult patients who have been diagnosed with myelodysplastic syndromes, when all of the following apply:
- you need regular blood transfusions to treat low levels of red blood cells (‘transfusion-dependent anaemia’)
- you have an abnormality of cells in the bone marrow called an ‘isolated deletion 5q cytogenic abnormality’. This means your body does not make enough healthy blood cells
- other treatments have been used before, are not suitable or do not work well enough.

Revlimid can increase the number of healthy red blood cells that the body produces by reducing the number of abnormal cells:
- This can reduce the number of blood transfusions needed. It is possible that no transfusions will be needed.

**How Revlimid works**
Revlimid works by affecting the body’s immune system and directly attacking the cancer. It works in a number of different ways:
- by stopping the cancer cells developing
- by stopping blood vessels growing in the cancer
- by stimulating part of the immune system to attack the cancer cells.

2. **What you need to know before you take Revlimid**

**Do not take Revlimid:**
- if you are pregnant or think you may be pregnant or are planning to become pregnant, as Revlimid is expected to be harmful to an unborn child (see section 2, “Warnings and precautions” and “Pregnancy and breast-feeding”).
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2, “Warnings and precautions” and “Pregnancy and breast-feeding”). If you are able to become pregnant, your doctor will record with each prescription that the necessary measures have been taken and will provide you with this confirmation.
- if you are allergic to lenalidomide or any of the other ingredients of this medicine listed in section 6. If you think you may be allergic, ask your doctor for advice.

If any of these apply to you, do not take Revlimid. Talk to your doctor if you are not sure.

**Warnings and precautions**

**Tell your doctor before starting treatment if you have:**
- had blood clots in the past - you have an increased risk of developing blood clots in the veins and arteries during treatment
any signs of an infection, such as a cough or fever
kidney problems - your doctor may adjust your dose of Revlimid
had a heart attack, have ever had a blood clot, or if you smoke, have high blood pressure or high cholesterol levels
a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure (this condition is called ‘Tumour Lysis Syndrome’)
had an allergic reaction whilst taking thalidomide such as rash, itching, swelling, dizziness or trouble breathing

If any of the above apply to you, tell your doctor before starting treatment.

If you have myelodysplastic syndromes, you may be more likely to get a more advanced condition called acute myeloid leukaemia (AML). In addition, we do not know how Revlimid affects the chances of you getting AML. Your doctor may therefore do tests to check for signs which may better predict the likelihood of getting AML during your treatment with Revlimid.

Tests and checks
Before and during the treatment with Revlimid you will have regular blood tests as Revlimid may cause a fall in the blood cells that help fight infection (white blood cells) and help the blood to clot (platelets). Your doctor should ask you to have a blood test:
- before treatment
- every week for the first 8 weeks of treatment
- at least every month after that.
Your doctor may check you for changes to your skin such as red spots or rashes.

Your doctor may adjust your dose of Revlimid or stop your treatment based on the results of your blood tests and on your general condition. If you are newly diagnosed, your doctor may also assess your treatment based on your age and other conditions you may already be experiencing.

Blood donation
You should not donate blood during treatment and for 1 week after the end of treatment.

Children and adolescents
Revlimid is not recommended for use in children and adolescents under 18 years.

Other medicines and Revlimid
Tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription including herbal medicines. This is because Revlimid can affect the way some other medicines work. Also, some other medicines can affect the way Revlimid works.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- some medicines used to prevent pregnancy such as oral contraceptives, as they may stop working
- some medicines used for heart problems – such as digoxin
- some medicines used to thin the blood – such as warfarin

Pregnancy, breast-feeding and contraception - information for women and men

Pregnancy
For women taking Revlimid
- You must not take Revlimid if you are pregnant, as it is expected to be harmful for an unborn baby.
- You must not become pregnant while taking Revlimid. Therefore you must use effective methods of contraception if you are a woman of childbearing potential (see “Contraception” below).
- If you do become pregnant during the treatment with Revlimid, you must stop the treatment and inform your doctor immediately.
For men taking Revlimid

- If your partner becomes pregnant whilst you are taking Revlimid, you should inform your doctor immediately. It is recommended that your partner seeks medical advice.
- You must also use effective methods of contraception (see “Contraception” below).

Breast-feeding
You should not breast-feed when taking Revlimid, as it is not known if Revlimid passes into human milk.

Contraception

For women taking Revlimid
Before starting the treatment, you should ask your doctor if you are able to become pregnant, even if you think this is unlikely.

If you are able to become pregnant
- you will have pregnancy tests under the supervision of your doctor (before every treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except where it has been confirmed that the fallopian tubes have been severed and sealed, to stop eggs from reaching the uterus (tubal sterilisation)
AND
- you must use effective methods of contraception for 4 weeks before starting treatment, during treatment, and until 4 weeks after stopping treatment. Your doctor will advise you on appropriate methods of contraception.

For men taking Revlimid
Revlimid passes into human semen. If your female partner is pregnant or able to become pregnant, and she does not use effective methods of contraception, you must use condoms during treatment and 1 week after the end of treatment, even if you have had a vasectomy.

Driving and using machines
Do not drive or operate machines if you feel dizzy, tired, sleepy or have blurred vision.

Revlimid contains lactose
Revlimid contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking Revlimid.

3. How to take Revlimid

Revlimid must be given to you by healthcare professionals with experience in treating multiple myeloma or myelodysplastic syndromes.

- When used to treat multiple myeloma, Revlimid is taken in combination with other medicines (see section 1 “What Revlimid is used for”).
- When used to treat myelodysplastic syndromes, it is taken alone.

Always take Revlimid alone or Revlimid in combination with other medicines exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If you are taking Revlimid in combination with other medicines, you should refer to the package leaflets for these medicines for further information on their use and effects.

Treatment cycle
Revlimid and the medicines you take in combination with Revlimid are taken on certain days over 4 weeks (28 days).

- Each 28 days is called a ‘treatment cycle’.
- Depending on the day of the cycle, you will take one or more of the medicines. However, on some days you do not take any of the medicines.
After completing each 28 day cycle, you should start a new ‘cycle’ over the next 28 days.

How much Revlimid to take
Before you start treatment, your doctor will tell you:
- how much Revlimid you should take
- how much of the other medicines you should take in combination with Revlimid, if any
- on what days of your treatment cycle to take each medicine.

Your doctor may also decide to adjust your dose of Revlimid or other medicines during treatment. This will be based on the results of your blood tests and on your general condition (see section 2 “What you need to know before you take Revlimid”).

How and when to take Revlimid
- Swallow the capsules whole, preferably with water.
- Do not break, open or chew the capsules.
- The capsules can be taken either with or without food.
- You should take Revlimid at about the same time on the scheduled days.

Duration of the treatment with Revlimid
Revlimid is taken in treatment cycles, each cycle lasting 28 days (see above “Treatment cycle”). You should continue the cycles of treatment until your doctor tells you to stop.

If you take more Revlimid than you should
If you take more Revlimid than was prescribed, tell your doctor immediately.

If you forget to take Revlimid
If you forget to take Revlimid at your regular time and
- less than 12 hours have passed: take your capsule immediately.
- more than 12 hours have passed: do not take your capsule. Take your next capsule at the usual time the next day.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Revlimid can cause side effects, although not everybody gets them.

Serious side effects which may affect more than 1 in 10 people
Revlimid may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders e.g. nosebleeds and bruising. Revlimid may also cause blood clots in the veins (thrombosis).

Therefore you must tell your doctor immediately if you experience:
- fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection (including within the bloodstream (sepsis))
- bleeding or bruising in the absence of injury
- chest pain or leg pain
- shortness of breath

If you experience any of the above side effects, tell your doctor immediately.

Other side effects are given below
It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with Revlimid treatment, therefore your doctor should carefully evaluate the benefit and risk when you are prescribed Revlimid.
Very common side effects may affect more than 1 in 10 people:

- A fall in the number of red blood cells which may cause anaemia leading to tiredness and weakness
- Constipation, diarrhoea, nausea, redness of skin, rashes, vomiting, muscle cramps, muscle aches, bone pain, joint pain, tiredness, generalised swelling including swelling of your arms and legs
- Fever and flu like symptoms including fever, muscle ache, headache, earache and chills
- Numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor, changes in the way things taste
- Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting, which may be symptoms of a heart attack (myocardial infarction)
- Decreased appetite
- Low levels of potassium in the blood
- Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism)
- Infections of all types
- Infection of the lung and the upper respiratory tract, shortness of breath
- Blurred vision
- Clouding of your eye (cataract)
- Kidney problems
- Changes to a protein in the blood that can cause swelling of the arteries (vasculitis)
- Increases in your blood sugar level (diabetes)
- Headache
- Dry skin
- Stomach pain
- Mood change, difficulty sleeping

Common side effects may affect up to 1 in 10 people:

- Bleeding from the gums, stomach, or bowels
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Darkening of your skin
- Skin eruptions, skin cracking, flaking or peeling skin
- Hives, itching, increased sweating, dehydration
- Sore inflamed mouth, dry mouth, difficulty swallowing
- Heartburn
- Production of much more or much less urine than usual (which may be a symptom of kidney failure), passing blood in the urine
- Shortness of breath especially when lying down (which may be a symptoms of heart failure)
- Difficulty getting an erection
- Stroke, fainting
- Muscle weakness
- Joint swelling
- Changes to blood thyroid hormone, low levels of calcium, phosphate or magnesium in the blood
- Depression
- Deafness
- Abnormal liver test results
- Impaired balance, movement difficulty
- Ringing in the ears (tinnitus)
- Iron overload
- Thirst
- Confusion
- Toothache
- Weight loss

Uncommon side effects may affect up to 1 in 100 people:

- Bleeding within the skull
- Circulatory problems
• Loss of vision
• Loss of sex drive (libido)
• Passing large amount of urine with bone pain and weakness, which may be symptoms of a kidney disorder (Fanconi syndrome)
• Stomach pain, bloating, or diarrhoea, which may be symptoms of inflammation in the large intestine (called colitis or caecitis)
• Passing much more or much less urine than usual, which may be a symptom of a type of kidney problem (called renal tubular necrosis)
• Changes to the colour of your skin, sensitivity to sunlight
• Certain types of skin tumour
• Hives, rashes, swelling of eyes, mouth or face, difficulty breathing, or itching, which may be symptoms of an allergic reaction

Rare side effects may affect up to 1 in 1,000 people:
• Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).
• Tumour lysis syndrome - metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heart beat, seizures, and sometimes death.

Not known: frequency cannot be estimated from the available data:
• Sudden, or mild but worsening pain in the upper abdomen and/or back, which remains for a few days, possibly accompanied by nausea, vomiting, fever and a rapid pulse. These symptoms may be due to inflammation of the pancreas.
• Wheezing, shortness of breath or a dry cough, which may be symptoms caused by inflammation of the tissue in the lungs.
• Yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale coloured stools, dark coloured urine, skin itch, rash, pain or swelling of the abdomen – these may be symptoms of injury to the liver (hepatic disorder).
• Rare cases of muscle breakdown (muscle pain, weakness or swelling) which can lead to kidney problems (rhabdomyolysis) have been observed, some of them when Revlimid is administered with a statin (a type of cholesterol lowering medication).
• A condition affecting the skin caused by inflammation of small blood vessels, along with pain in the joints and fever (leukocytoclastic vasculitis).
• Breakdown of the wall of the stomach or intestine. This may lead to very serious infection. Tell your doctor if you have severe abdominal pain, fever, nausea, vomiting, blood in your stool, or changes in bowel habits.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Revlimid
• Keep this medicine out of the sight and reach of children.
• Do not use this medicine after the expiry date, which is stated on the blister and on the carton after “EXP”. The expiry date refers to the last day of that month.
• This product does not require any special storage conditions.
• Do not use this medicine if you notice any damage or signs of tampering to the pack.
• Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to through away medicines you no longer use. These measures will help protect the environment.
6. Content of the pack and other information

What Revlimid contains

Revlimid 2.5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 2.5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171), indigo carmine (E132) and yellow iron oxide (E172)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine and titanium dioxide (E171)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 7.5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 7.5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171) and yellow iron oxide (E172)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 10 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 10 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171), indigo carmine (E132) and yellow iron oxide (E172)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 15 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 15 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171) and indigo carmine (E132)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 20 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 20 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine and titanium dioxide (E171), indigo carmine (E132) and yellow iron oxide (E172)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).
Revlimid 25 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 25 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine and titanium dioxide (E171)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

What Revlimid looks like and contents of the pack

Revlimid 2.5 mg hard capsules are blue-green/white, with “REV 2.5 mg” written on them. The capsules are provided in packs. Each pack contains one or three blisters, each blister with seven capsules. This gives a total of 7 or 21 capsules per pack.

Revlimid 5 mg hard capsules are white, with “REV 5 mg” written on them. The capsules are provided in packs. Each pack contains one or three blisters, each blister with seven capsules. This gives a total of 7 or 21 capsules per pack.

Revlimid 7.5 mg hard capsules are pale yellow/white, with “REV 7.5 mg” written on them. The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

Revlimid 10 mg hard capsules are blue-green/pale yellow, with “REV 10 mg” written on them. The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

Revlimid 15 mg hard capsules are pale blue/white, with “REV 15 mg” written on them. The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

Revlimid 20 mg hard capsules are blue-green/pale blue, with “REV 20 mg” written on them. The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

Revlimid 25 mg hard capsules are white, with “REV 25 mg” written on them. The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

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Other sources of information:

Please contact the Marketing Authorisation Holder if you require this information in another format.

Detailed information on this medicine is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.

There are also links to other websites about rare diseases and treatments.