

Understanding VIDAZA

**A patient's
guide to
VIDAZA®**



vidaza®
azacitidine for injection

Introduction

This guide provides information about VIDAZA® and what to expect during treatment. Terms in **green** are defined in the glossary on pages 21-23.

If you have any questions about **myelodysplastic syndromes** (MY•eh•loh•dis•PLAS•tik SIN•dromz) **(MDS)** or VIDAZA after reading this guide, be sure to talk to your doctor or nurse.

For a list of MDS resources, see pages 19–20.

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).



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Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Understanding MDS

What is MDS?

Myelodysplastic syndromes (MDS) are a group of diseases that affect the blood and **bone marrow** (bone MAYR•oh). Bone marrow is the soft, sponge-like tissue in the center of the bones that makes blood cells. In people with MDS, the bone marrow makes abnormal cells and does not make enough healthy blood cells.

People living with MDS typically have low blood cell counts. This means their bone marrow makes abnormally low levels of **red blood cells (RBCs)**, **white blood cells (WBCs)**, and/or **platelets** (PLATE•lets). These low levels of blood cells are called **cytopenias** (SY•toh•PEE•nee•uhs).

- Low RBC levels—**anemia** (a•NEE•mee•a)—May make you feel tired, weak, or short of breath
- Low WBC levels—**neutropenia** (noo•troh•PEE•nee•uh)—May increase your risk for infections and cause fever or mouth sores
- Low platelet levels—**thrombocytopenia** (THROM•boh•sy•toh•PEE•nee•uh)—May cause you to bruise more easily, or bleed for no reason (a nosebleed or bleeding gums from teeth brushing)

MDS can cause other health problems. It is important to discuss the risks of these problems with your doctor or nurse. Report bleeding and infections to them right away. You should also ask your doctor if you have a risk of developing a cancer of the blood and bone marrow called **leukemia** (loo•KEE•mee•uh).

At some point, most patients with MDS will receive **supportive care** (suh•POR•tiv kayr). Supportive care does not change the progression of MDS, but is used to reduce some of the signs or symptoms. One of the most common examples of supportive care is a blood **transfusion** (trans•FYOO•zhun). This process adds parts of blood or whole blood into the bloodstream.

What are the risks involved with blood transfusions?

If you have MDS and are receiving blood transfusions, you know they can take several hours to receive. While they can be very beneficial, they also come with risks:

- **Iron overload**—Each time you receive an RBC transfusion, you're adding small amounts of iron to your blood. The iron can build up and harm your liver, heart, and/or pancreas
- **Transfusion reactions**—The more transfusions you receive, the higher your risk of a transfusion reaction. Your immune system may react to transfused blood cells as if they should not be in your body. When this happens, your own blood makes **antibodies** (AN•tee•BAH•dees) to reject the new blood cells. This causes a transfusion reaction, usually mild, but sometimes serious
- **Infection**—There is a chance you could get an infection from a transfusion. Your doctor may prescribe an **antibiotic** (an•tih•by•AH•tik) to treat an infection

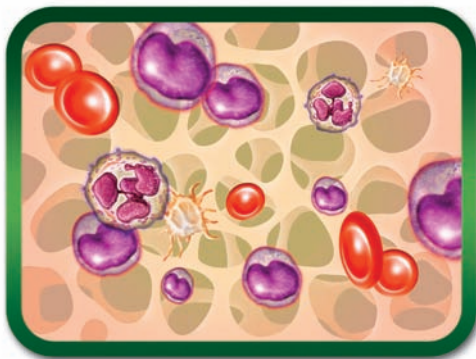
In spite of these risks, transfusions offer patients with MDS the important benefit of temporary relief from symptoms of anemia and/or thrombocytopenia. Be sure to discuss the risks and benefits of transfusions with your doctor.

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

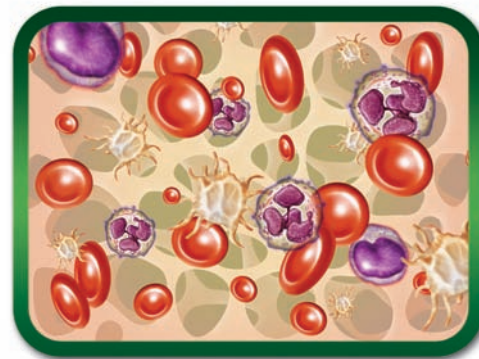
Understanding VIDAZA®

How does VIDAZA treat MDS?

When you have MDS, your bone marrow usually makes fewer healthy blood cells. The blood cells it *does* make don't always work as they should. VIDAZA was the first drug approved by the US Food and Drug Administration (FDA) for the treatment of all 5 FAB subtypes of MDS. VIDAZA may be able to help your bone marrow make healthy blood cells again.



Bone marrow in a person with MDS



Healthy bone marrow

There are different ways of classifying MDS. One system (International Prognostic Scoring System or IPSS) uses cell type and blood counts of patients with MDS to predict the course of their disease. This system separates patients into lower-risk and higher-risk categories. This helps doctors determine the treatment plan for each patient.

Another system (French-American-British or FAB) divides MDS into 5 groups called subtypes. VIDAZA is used to treat patients with all 5 FAB subtypes. Your doctor can explain which subtype of MDS you have.

The 5 FAB MDS subtypes that VIDAZA treats are:

- **RA, refractory anemia*** (ree•FRAK•tuh•ree a•NEE•mee•a), or **RARS**, refractory anemia with **ringed sideroblasts** (ringd SID•eh•ro•blasts)—With RA or RARS, you have less than 5% **blasts** or immature cells in the bone marrow and at least 1 cytopenia (abnormally low blood cell count [usually RBCs]). About 40% of patients with MDS have RA or RARS
- **RAEB**, refractory anemia with excess blasts[†]—With RAEB, you have 5% to 20% blasts in the bone marrow and at least 2 cytopenias (low counts of at least 2 types of blood cells [for example, RBCs and platelets]). About 30% of patients with MDS have RAEB
- **RAEB-T**, refractory anemia with excess blasts in transformation—With RAEB-T, you have between 21% and 30% blasts in the bone marrow and at least 2 cytopenias. This form of MDS may turn into a type of cancer of the blood and bone marrow called **acute myeloid leukemia** (uh•KYOOT MY•eh•loid loo•KEE•mee•uh) (**AML**). About 20% of patients with MDS have RAEB-T
- **CMMoL, chronic myelomonocytic leukemia** (KRAH•nik MY•eh•loh•MAH•noh•SIH•tik loo•KEE•mee•uh)—With CMMoL, you have between 5% and 20% blasts in the bone marrow and an increased number of **monocytes** (MAH•noh•sytz), a type of WBC. About 10% of patients with MDS have CMMoL

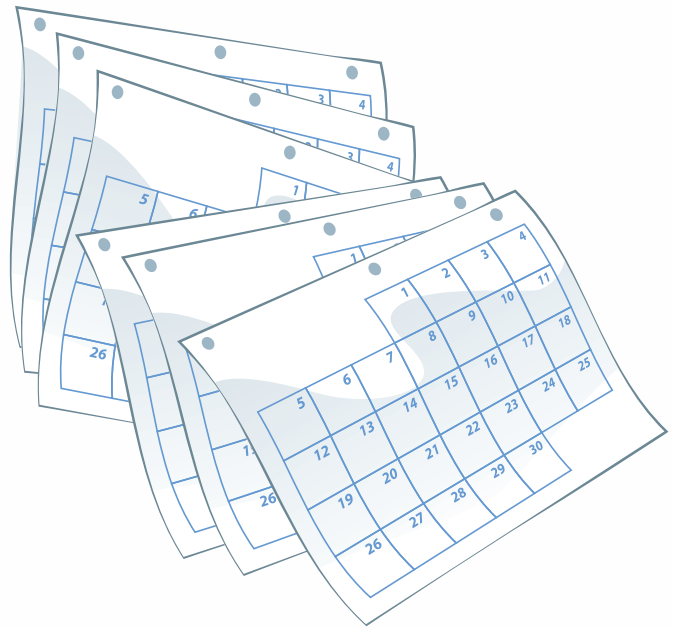
*Refractory anemia = low blood cell amounts that do not respond to supportive care.

[†]Excess blasts = increased number of immature blood cells in the bone marrow.

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Why was VIDAZA® prescribed?

Your doctor may have prescribed VIDAZA to help reduce your need for RBC transfusions. VIDAZA may also help your bone marrow make healthy WBCs and platelets. Your doctor may prescribe VIDAZA for as long as you continue to benefit from it and side effects don't require that you stop treatment. Always follow your doctor's recommendations about continuing your treatment plan. If you stop receiving VIDAZA, your symptoms may return.



Knowing what to expect during treatment

How is VIDAZA given?

VIDAZA can be given as a **subcutaneous** (sub•kyoo•TAY•nee•us) injection. It can also be given as an **intravenous** (IN•truh•VEE•nus) or IV infusion. You are likely to be given medication to prevent nausea and vomiting.

Subcutaneous injection

A subcutaneous injection is similar to the way people with diabetes take their insulin each day. Injection sites, or areas where the injection can be given, include the thigh, stomach, or upper arm.

Using a small needle, the nurse injects VIDAZA into the layer of fat just under the skin. It is not a deep injection. It should not go into a muscle or vein.

When you are treated with VIDAZA, you may need to receive more than 1 injection daily (usually 2). Your doctor or nurse will use a different site for each injection. VIDAZA should be given by a trained nurse or doctor in a doctor's office, clinic, or hospital.

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.



IV infusion

When you receive VIDAZA® through an IV infusion, it is injected into a bag. Then it is delivered into your vein through a tube, which is usually attached to your lower arm. The word intravenous means “within a vein.” An IV infusion is a fast way to deliver medication directly to your bloodstream. The bloodstream then carries the medication throughout your body immediately.

To give you an IV infusion of VIDAZA, your nurse or doctor will insert a needle into your vein. The VIDAZA solution will infuse (run in) for 10 to 40 minutes.

Can I give myself VIDAZA at home?

No. It should be given by a trained nurse or doctor in a doctor’s office, clinic, or hospital. The doctor or nurse will monitor you before treatment and watch for any reaction you may have to the treatment.



How often will I receive VIDAZA?

You will visit your doctor's office daily for 7 days to receive VIDAZA through a subcutaneous injection or an IV infusion. An injection can be given in a few minutes each day. An IV infusion can take from 10 to 40 minutes each day. Then you will have 21 days without treatment. Each 28-day period (the 7 days you receive VIDAZA plus the 21 days you do not) is called a "cycle" of treatment. Your doctor will look at your blood counts and other factors as you receive treatment with VIDAZA. If your doctor decides it is necessary, he or she may extend your treatment cycle to longer than 28 days.

How long will I be on VIDAZA?

VIDAZA is not a one-time treatment. Treatment cycles are given every 28 days for as long as your doctor recommends them. It may take several cycles (about 4 to 6 months) for your doctor to notice a difference. If you stop receiving treatment, your symptoms may return. Therefore, your doctor may want to keep you on it for as long as you continue to benefit from it and side effects don't require you to stop it.

While you're on VIDAZA your blood cell counts may fall during your first few cycles of treatment. This may cause you to feel tired or have a fever. Always follow your doctor's recommendations about continuing your treatment plan. By cycle 3 or 4, VIDAZA may be helping your bone marrow make healthy blood cells. As a result, your blood cell counts may begin to rise. By cycles 4-6, your need for transfusions may be decreased. That means you may feel less tired and have fewer fevers.

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Important Safety Information

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).

Important Safety Information

- VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol and in patients with advanced malignant hepatic tumors
- In Studies 1 and 2, the most commonly occurring adverse reactions by SC route were nausea (70.5%), anemia (69.5%), thrombocytopenia (65.5%), vomiting (54.1%), pyrexia (51.8%), leukopenia (48.2%), diarrhea (36.4%), injection site erythema (35.0%), constipation (33.6%), neutropenia (32.3%), and ecchymosis (30.5%). Other adverse reactions included dizziness (18.6%), chest pain (16.4%), febrile neutropenia (16.4%), myalgia (15.9%), injection site reaction (13.6%), and malaise (10.9%). In Study 3, the most common adverse reactions by IV route also included petechiae (45.8%), weakness (35.4%), rigors (35.4%), and hypokalemia (31.3%)
- In Study 4, the most commonly occurring adverse reactions were thrombocytopenia (69.7%), neutropenia (65.7%), anemia (51.4%), constipation (50.3%), nausea (48.0%), injection site erythema (42.9%), and pyrexia (30.3%). The most commonly occurring Grade 3/4 adverse reactions were neutropenia (61.1%), thrombocytopenia (58.3%), leukopenia (14.9%), anemia (13.7%), and febrile neutropenia (12.6%)
- Because treatment with VIDAZA is associated with anemia, neutropenia, and thrombocytopenia, complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle
- Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. In addition, azacitidine and its metabolites are substantially excreted by the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function
- VIDAZA may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be apprised of the potential hazard to the fetus. Men should be advised not to father a child while receiving VIDAZA
- Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother

Please see enclosed full Prescribing Information.

Side effects

Understanding side effects

Report any side effects to your doctor or nurse as soon as they happen. Talk to your doctor if you are nauseated or vomiting. Your doctor will likely give you medication along with VIDAZA to help reduce these side effects.

Some side effects related to VIDAZA, including a reduced blood cell count, may lessen after the first few treatment cycles. It is important to tell your doctor or nurse about any side effects you may have so that you can discuss your treatment plan.

The most common side effects by subcutaneous injection include:

- Nausea
- Anemia
- Thrombocytopenia
- Vomiting
- Fever
- Diarrhea
- Redness of the skin at the injection site
- Constipation
- Neutropenia
- Bruising of the skin at the injection site

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

The most common side effects for an IV infusion are the same as those for a subcutaneous injection, but also include:

- Small reddish-purple spots on the body
- Chills
- Weakness
- Low potassium in the blood, or **hypokalemia** (HI•po•ka•LEE•mee•a)

Other side effects may occur, such as:

- Dizziness
- Chest pain
- **Febrile neutropenia** (FEH•brile noo•troh•PEE•nee•uh)
- **Myalgia** (my•AL•juh)
- Injection site reaction
- **Malaise** (muh•LAYZ)

Myelosuppression

In some patients, treatment with VIDAZA® may cause **myelosuppression** (MY•eh•loh•suh•PREH•shun). This common condition causes bone marrow to make fewer blood cells than normal. Myelosuppression can cause any or all of the following:

- Reduced RBC counts, also called anemia—This may make you feel tired
- Reduced WBC counts, also called neutropenia—This may make you more likely to get an infection
- Reduced platelet counts, also called thrombocytopenia—This may cause bleeding for no reason (such as nosebleeds or bleeding gums)

Be sure to ask your doctor or nurse about any symptoms you may have or other side effects that may occur. It is important to tell your doctor or nurse about any side effects you may have so that you can discuss your treatment plan.

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Nausea and vomiting

Nausea and vomiting are the most common side effects of treatment with VIDAZA®. They can be controlled in most patients. Your doctor will likely give you medicine before your treatment to help control these symptoms.

In addition, these tips may help with nausea and vomiting:

- Breathe deeply and slowly if you start to feel ill
- Eat several small meals daily instead of 3 large ones
- Avoid sweet, fried, or fatty foods
- To avoid cooking odors, eat foods cold or at room temperature
- Eat dry foods like toast (even before getting out of bed) if you feel ill in the mornings
- Drink cool, clear, unsweetened fruit juices. You might try apple juice or light-colored sodas, like ginger ale,* that have lost their fizz
- Wear loose clothing
- Try ginger tea, fresh ginger, and candied ginger*

*Ginger may affect blood clotting. Be sure to let your doctor know if you are eating or drinking any products that contain ginger.

Injection site reactions

Another common side effect of treatment is an injection site reaction. An injection site reaction can be anything from a bruise to a large, painful, red welt. Injection site reactions usually go away after several days.

In addition, these tips may help with injection site reactions:

- If an injection site is painful or red, apply a compress for 15 minutes at a time. You may use a cool or warm compress, whichever is more comfortable
- **Do not use hot compresses; these may make your symptoms worse or make your skin blister at the injection site**
- **Do not ice the injection site; this may affect how VIDAZA gets into your bloodstream**
- When receiving VIDAZA treatment, you may want to ask the doctor or nurse to find places where you can get your injection that will not be rubbed by your clothing (such as a belt). Remember that other items (such as seat belts or elastic waistbands) could make you uncomfortable

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Other considerations

What else do I need to know about treatment with VIDAZA®?

As you receive treatment with VIDAZA, remember:

- **Routine blood tests**—Before each cycle of treatment, you will need to have a blood test. Blood tests help your doctor understand how well VIDAZA is working. They will also help your doctor take care of any side effects of treatment
- **Pregnancy and nursing**—Women should not become pregnant or breastfeed while receiving VIDAZA. Men should avoid fathering a child while receiving VIDAZA
- **Liver problems**—Tell your doctor if you have liver problems before receiving VIDAZA
- **Kidney problems**—Tell your doctor if you have kidney problems before receiving VIDAZA

Seeking additional support

What groups or foundations can give me more information about MDS?

- **American Cancer Society (ACS)**
1-800-ACS-2345 (1-800-227-2345)
www.cancer.org
- **Aplastic Anemia & MDS International Foundation, Inc.**
1-800-747-2820
www.aamds.org
- **Leukemia & Lymphoma Society**
1-800-955-4572
www.lls.org
- **Leukemia Research Foundation**
1-888-558-5385
www.leukemia-research.org
- **Myelodysplastic Syndromes Foundation**
1-800-MDS-0839 (1-800-637-0839)
www.mds-foundation.org
- **National Cancer Institute**
1-800-4-CANCER (1-800-422-6237)
www.cancer.gov

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Where can I get more information about VIDAZA®?

- Visit www.VIDAZA.com
- **Celgene Corporation**
www.celgene.com

What if I can't pay for treatment?

Celgene Corporation is committed to helping patients who can't afford treatment with VIDAZA. Help may be available for patients without insurance or whose insurance does not cover VIDAZA. Help may also be available for patients who have been denied access to federal- or state-funded assistance programs.

To learn more about the Celgene Patient Assistance Program, call **1-800-931-8691** Monday through Friday, between 8 AM and 7 PM ET.

Increasing your understanding

Glossary

Definitions of the terms **(green)** used in this guide appear below.

acute myeloid leukemia (uh•KYOOT MY•eh•loid loo•KEE•mee•uh) **(AML)**—A type of cancer in which too many immature WBCs are found in the blood and bone marrow. “Acute” means that the leukemia develops quickly and becomes worse (See *leukemia*)

anemia (a•NEE•mee•a)—A condition in which the number of RBCs is below normal

antibiotic (an•tih•by•AH•tik)—A medicine that helps prevent or control infection

antibodies (AN•tee•BAH•dees)—Proteins found in the blood. They are made in response to foreign substances that invade the body. Antibodies protect the body from disease by binding to these foreign substances and destroying them

blasts—Immature blood cells that become RBCs, WBCs, or platelets

bone marrow (bone MAYR•oh)—The soft, sponge-like tissue in the center of bones that makes RBCs, WBCs, and platelets

chronic myelomonocytic leukemia

(KRAH•nik MY•eh•loh•MAH•noh•SIH•tik loo•KEE•mee•uh) **(CMMoL)**—A slowly progressing type of cancer in which too many myelomonocytes (a type of WBC) are in the bone marrow

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

cytopenias (SY•toh•PEE•nee•uhs)—Reductions in the number of blood cells

febrile neutropenia (FEH•brile noo•troh•PEE•nee•uh)—Fever combined with a significant reduction (or decrease) in WBCs (neutropenia) needed to fight infection

hypokalemia (HI•po•ka•LEE•mee•a)—Low potassium in the blood

intravenous (IN•truh•VEE•nus)—Within a vein

leukemia (loo•KEE•mee•uh)—Cancer of the blood and bone marrow

malaise (muh•LAYZ)—A general, or overall, feeling of discomfort

monocytes (MAH•noh•sytz)—Large, circulating WBCs that are formed in the bone marrow

myalgia (my•AL•juh)—Pain in one or several muscles

myelodysplastic syndromes (MY•eh•loh•dis•PLAS•tik SIN•dromz) (**MDS**)—Derived from *myelo*, which means marrow, and *dysplasia*, which means abnormal growth. A group of diseases in which the bone marrow does not make enough healthy blood cells

myelosuppression (MY•eh•loh•suh•PREH•shun)—This condition prevents or slows the bone marrow's production of blood cells

neutropenia (noo•troh•PEE•nee•uh)—A condition in which the number of neutrophils (the most numerous type of WBC that helps fight infection) is below normal in the blood

platelets (PLATE•lets)—Blood cells that are essential for blood clotting

red blood cells (RBCs)—The cells that carry oxygen to the body’s tissues

refractory anemia (ree•FRAK•tuh•ree a•NEE•mee•a)—Anemia resistant to treatment

ringed sideroblasts (ringd SID•eh•ro•blasts)—RBCs that contain an iron protein complex called ferritin. The amount of ferritin in your blood helps your doctor determine how much iron is stored in your blood

subcutaneous (sub•kyoo•TAY•nee•us)—Under the skin

supportive care (suh•POR•tiv kayr)—Treatment that reduces the symptoms of the disease but does not change the course of the disease

thrombocytopenia (THROM•boh•sy•toh•PEE•nee•uh)—A condition in which the number of platelets, or thrombocytes, is below normal, resulting in the tendency to bruise and bleed more easily

transfusion (trans•FYOO•zhun)—Adds parts of blood or whole blood into the bloodstream

white blood cells (WBCs)—The cells that help the body fight infection

Please see Important Safety Information on page 12 and enclosed full Prescribing Information.

Contact information

Doctor: _____

Phone number: _____

Nurse: _____

Phone number: _____



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A decorative graphic in the bottom right corner featuring a yellow leaf-like shape, a blue wavy line, and a green-to-yellow gradient background.

vidaza®
azacitidine for injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIDAZA safely and effectively. See full prescribing information for VIDAZA.

VIDAZA (azacitidine for injection) for SC or IV use

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

VIDAZA is a nucleoside metabolic inhibitor indicated for the treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology values, is VIDAZA 75 mg/m² daily for 7 days to be administered by subcutaneous (SC) injection or intravenous (IV) infusion. Premedicate for nausea and vomiting. (2.1)
- Repeat cycles every 4 weeks (2.2). After 2 cycles, may increase dose to 100 mg/m² if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred (2.2). Patients should be treated for a minimum of 4 to 6 cycles. Complete or partial response may require additional treatment cycles (2.2).
- Continue treatment as long as the patient continues to benefit (2.2).
- Patients should be monitored for hematologic response and renal toxicities, with dosage delay or reduction as appropriate (2.3, 2.4, 2.5).

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder in 100 mg single-use vials (3).

CONTRAINDICATIONS

- Advanced malignant hepatic tumors (4.1).
- Hypersensitivity to azacitidine or mannitol (4.2).

WARNINGS AND PRECAUTIONS

- Anemia, neutropenia and thrombocytopenia. Perform complete blood counts (CBC) prior to each treatment cycle and as needed to monitor response and toxicity (5.1).
- Hepatotoxicity: Use with caution in patients with severe preexisting liver impairment (5.2).
- Renal abnormalities. Monitor patients with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys (5.3).
- Monitor liver chemistries and serum creatinine prior to initiation of therapy and with each cycle (5.4).
- VIDAZA may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be apprised of the potential hazard to a fetus (5.5, 8.1).
- Men should be advised not to father a child while receiving VIDAZA (5.6, 13).

ADVERSE REACTIONS

Most common adverse reactions (>30%) by SC route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. Most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted (7).

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3).
- Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: August 2008

VidPlyPI.001 08/08

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Myelodysplastic Syndromes (MDS)

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).

2 DOSAGE AND ADMINISTRATION

2.1 First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m² subcutaneously or intravenously, daily for 7 days. Patients should be premedicated for nausea and vomiting.

2.2 Subsequent Treatment Cycles

Cycles should be repeated every 4 weeks. The dose may be increased to 100 mg/m² if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 to 6 cycles. However, complete or partial response may require additional treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Patients should be monitored for hematologic response and renal toxicities [see *Warnings and Precautions* (5.3)], and dosage delay or reduction as described below may be necessary.

2.3 Dosage Adjustment Based on Hematology Laboratory Values

- For patients with baseline (start of treatment) WBC $\geq 3.0 \times 10^9/L$, ANC $\geq 1.5 \times 10^9/L$, and platelets $\geq 75.0 \times 10^9/L$, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC ($\times 10^9/L$)	Platelets ($\times 10^9/L$)	
<0.5	<25.0	50%
0.5-1.5	25.0-50.0	67%
>1.5	>50.0	100%

- For patients whose baseline counts are WBC $< 3.0 \times 10^9/L$, ANC $< 1.5 \times 10^9/L$, or platelets $< 75.0 \times 10^9/L$, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
	% Dose in the Next Course		
50-75	100	50	33
>75	75	50	33

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are $>25\%$ above the nadir and rising. If a $>25\%$ increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the patient should be treated with 50% of the scheduled dose.

2.4 Dosage Adjustment Based on Renal Function and Serum Electrolytes

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course [see *Warnings and Precautions* (5.3)].

2.5 Use in Geriatric Patients

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.5)].

2.6 Preparation of VIDAZA

VIDAZA is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing VIDAZA suspensions [see *How Supplied/Storage and Handling* (16)].

If reconstituted VIDAZA comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

The VIDAZA vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly [see *How Supplied/Storage and Handling* (16)]. Do not save any unused portions for later administration.

2.7 Instructions for Subcutaneous Administration

VIDAZA should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

VIDAZA suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Suspension Stability: VIDAZA reconstituted for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F).

2.8 Instructions for Intravenous Administration

Reconstitute the appropriate number of VIDAZA vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of VIDAZA solution to deliver the desired dose and inject into a 50 - 100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Solution Incompatibility

VIDAZA is incompatible with 5% Dextrose solutions, Hespán, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of VIDAZA and should therefore be avoided.

Intravenous Administration

VIDAZA solution is administered intravenously. Administer the total dose over a period of 10 - 40 minutes. The administration must be completed within 1 hour of reconstitution of the VIDAZA vial.

Solution Stability: VIDAZA reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

3 DOSAGE FORMS AND STRENGTHS

VIDAZA (azacitidine for injection) is supplied as lyophilized powder in 100 mg single-use vials.

4 CONTRAINDICATIONS

4.1 Advanced Malignant Hepatic Tumors

VIDAZA is contraindicated in patients with advanced malignant hepatic tumors [see *Warnings and Precautions* (5.2)].

4.2 Hypersensitivity to Azacitidine or Mannitol

VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia, Neutropenia and Thrombocytopenia

Treatment with VIDAZA is associated with anemia, neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and hematologic response [see *Dosage and Administration* (2.3)].

5.2 Severe Preexisting Hepatic Impairment

Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors [see *Contraindications* (4.1)].

Safety and effectiveness of VIDAZA in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.

5.3 Renal Abnormalities

Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported rarely in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for nonMDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held [see Dosage and Administration (2.4)].

Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys [see Dosage and Administration (2.4, 2.5)].

Safety and effectiveness of VIDAZA in patients with MDS and renal impairment have not been studied as these patients were excluded from the clinical trials.

5.4 Monitoring Laboratory Tests

Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of therapy.

5.5 Pregnancy

Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine caused congenital malformations in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. There are no adequate and well-controlled studies in pregnant women using VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

5.6 Use in Males

Men should be advised to not father a child while receiving treatment with VIDAZA. In animal studies, pre-conception treatment of male mice and rats resulted in increased embryofetal loss in mated females [see Nonclinical Toxicology (13)].

6 ADVERSE REACTIONS

6.1 Overview

Adverse Reactions Described in Other Labeling Sections: anemia, neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma [see Warnings and Precautions (5.1, 5.2, 5.3)].

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC or IV Route):

Discontinuation: leukopenia, thrombocytopenia, neutropenia.

Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.

Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VIDAZA in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (SC administration), Studies 2 and 3 were single arm studies (one with SC administration and one with IV administration), and Study 4 was an international randomized trial (SC administration) [see Clinical Studies (14)].

In Studies 1, 2 and 3, a total of 268 patients were exposed to VIDAZA, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). VIDAZA was studied primarily in supportive-care controlled and uncontrolled trials (n=150 and n=118, respectively). The population in the subcutaneous studies (n=220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the IV study (n=48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 mg/m².

In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to VIDAZA. Of these patients, 119 were exposed for 6 or more cycles, and 63 for at least 12 cycles. The mean age of this population was 68.1 years (ranging from 42 to 83 years), 74% were male, and 99% were white. Most patients received daily VIDAZA doses of 75 mg/m².

Table 1 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA (SC) in Studies 1 and 2. It is important to note that duration of exposure was longer for the VIDAZA-treated group than for the observation group: patients received VIDAZA for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 1: Most Frequently Observed Adverse Reactions (≥5.0% in All SC VIDAZA Treated Patients; Studies 1 and 2)

System Organ Class Preferred Term ^a	Number (%) of Patients	
	All VIDAZA ^b (N=220)	Observation ^c (N=92)
Blood and lymphatic system disorders		
Anemia	153 (69.5)	59 (64.1)
Anemia aggravated	12 (5.5)	5 (5.4)
Febrile neutropenia	36 (16.4)	4 (4.3)
Leukopenia	106 (48.2)	27 (29.3)
Neutropenia	71 (32.3)	10 (10.9)
Thrombocytopenia	144 (65.5)	42 (45.7)
Gastrointestinal disorders		
Abdominal tenderness	26 (11.8)	1 (1.1)
Constipation	74 (33.6)	6 (6.5)
Diarrhea	80 (36.4)	13 (14.1)
Gingival bleeding	21 (9.5)	4 (4.3)
Loose stools	12 (5.5)	0
Mouth hemorrhage	11 (5.0)	1 (1.1)
Nausea	155 (70.5)	16 (17.4)
Stomatitis	17 (7.7)	0
Vomiting	119 (54.1)	5 (5.4)
General disorders and administration site conditions		
Chest pain	36 (16.4)	5 (5.4)
Injection site bruising	31 (14.1)	0
Injection site erythema	77 (35.0)	0
Injection site granuloma	11 (5.0)	0
Injection site pain	50 (22.7)	0
Injection site pigmentation changes	11 (5.0)	0
Injection site pruritus	15 (6.8)	0
Injection site reaction	30 (13.6)	0
Injection site swelling	11 (5.0)	0
Lethargy	17 (7.7)	2 (2.2)
Malaise	24 (10.9)	1 (1.1)
Pyrexia	114 (51.8)	28 (30.4)
Infections and infestations		
Nasopharyngitis	32 (14.5)	3 (3.3)
Pneumonia	24 (10.9)	5 (5.4)
Upper respiratory tract infection	28 (12.7)	4 (4.3)
Injury, poisoning, and procedural complications		
Post procedural hemorrhage	13 (5.9)	1 (1.1)
Metabolism and nutrition disorders		
Anorexia	45 (20.5)	6 (6.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	49 (22.3)	3 (3.3)
Chest wall pain	11 (5.0)	0
Myalgia	35 (15.9)	2 (2.2)
Nervous system disorders		
Dizziness	41 (18.6)	5 (5.4)
Headache	48 (21.8)	10 (10.9)
Psychiatric disorders		
Anxiety	29 (13.2)	3 (3.3)
Insomnia	24 (10.9)	4 (4.3)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	64 (29.1)	11 (12.0)

continued

System Organ Class Preferred Term ^a	Number (%) of Patients	
	All VIDAZA ^b (N=220)	Observation ^c (N=92)
Skin and subcutaneous tissue disorders		
Dry skin	11 (5.0)	1 (1.1)
Ecchymosis	67 (30.5)	14 (15.2)
Erythema	37 (16.8)	4 (4.3)
Rash	31 (14.1)	9 (9.8)
Skin nodule	11 (5.0)	1 (1.1)
Urticaria	13 (5.9)	1 (1.1)
Vascular disorders		
Hematoma	19 (8.6)	0
Hypotension	15 (6.8)	2 (2.2)
Petechiae	52 (23.6)	8 (8.7)

^a Multiple terms of the same preferred terms for a patient are only counted once within each treatment group.
^b Includes adverse reactions from all patients exposed to VIDAZA, including patients after crossing over from observations.
^c Includes adverse reactions from observation period only; excludes any adverse events after crossover to VIDAZA.

System Organ Class Preferred Term ^a	Number (%) of Patients			
	Any Grade		Grade 3/4	
	VIDAZA (N=175)	Best Supportive Care Only (N=102)	VIDAZA (N=175)	Best Supportive Care Only (N=102)
Investigations				
Weight decreased	14 (8.0)	0	1 (0.6)	0
Metabolism and nutrition disorders				
Hypokalemia	11 (6.3)	3 (2.9)	3 (1.7)	3 (2.9)
Nervous system disorders				
Lethargy	13 (7.4)	2 (2.0)	0	1 (1.0)
Psychiatric disorders				
Anxiety	9 (5.1)	1 (1.0)	0	0
Insomnia	15 (8.6)	3 (2.9)	0	0
Renal and urinary disorders				
Hematuria	11 (6.3)	2 (2.0)	4 (2.3)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	26 (14.9)	5 (4.9)	6 (3.4)	2 (2.0)
Dyspnea exertional	9 (5.1)	1 (1.0)	0	0
Pharyngolaryngeal pain	11 (6.3)	3 (2.9)	0	0
Skin and subcutaneous tissue disorders				
Erythema	13 (7.4)	3 (2.9)	0	0
Petechiae	20 (11.4)	4 (3.9)	2 (1.1)	0
Pruritus	21 (12.0)	2 (2.0)	0	0
Rash	18 (10.3)	1 (1.0)	0	0
Vascular disorders				
Hypertension	15 (8.6)	4 (3.9)	2 (1.1)	2 (2.0)

^a Multiple reports of the same preferred term from a patient were only counted once within each treatment.

Table 2 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA in Study 4. Similar to Studies 1 and 2 described above, duration of exposure to treatment with VIDAZA was longer (mean 12.2 months) compared with best supportive care (mean 7.5 months).

System Organ Class Preferred Term ^a	Number (%) of Patients			
	Any Grade		Grade 3/4	
	VIDAZA (N=175)	Best Supportive Care Only (N=102)	VIDAZA (N=175)	Best Supportive Care Only (N=102)
Blood and lymphatic system disorders				
Anemia	90 (51.4)	45 (44.1)	24 (13.7)	9 (8.8)
Febrile neutropenia	24 (13.7)	10 (9.8)	22 (12.6)	7 (6.9)
Leukopenia	32 (18.3)	2 (2.0)	26 (14.9)	1 (1.0)
Neutropenia	115 (65.7)	29 (28.4)	107 (61.1)	22 (21.6)
Thrombocytopenia	122 (69.7)	35 (34.3)	102 (58.3)	29 (28.4)
Gastrointestinal disorders				
Abdominal pain	22 (12.6)	7 (6.9)	7 (4.0)	0
Constipation	88 (50.3)	8 (7.8)	2 (1.1)	0
Dyspepsia	10 (5.7)	2 (2.0)	0	0
Nausea	84 (48.0)	12 (11.8)	3 (1.7)	0
Vomiting	47 (26.9)	7 (6.9)	0	0
General disorders and administration site conditions				
Fatigue	42 (24.0)	12 (11.8)	6 (3.4)	2 (2.0)
Injection site bruising	9 (5.1)	0	0	0
Injection site erythema	75 (42.9)	0	0	0
Injection site hematoma	11 (6.3)	0	0	0
Injection site induration	9 (5.1)	0	0	0
Injection site pain	33 (18.9)	0	0	0
Injection site rash	10 (5.7)	0	0	0
Injection site reaction	51 (29.1)	0	1 (0.6)	0
Pyrexia	53 (30.3)	18 (17.6)	8 (4.6)	1 (1.0)
Infections and infestations				
Rhinitis	10 (5.7)	1 (1.0)	0	0
Upper respiratory tract infection	16 (9.1)	4 (3.9)	3 (1.7)	0
Urinary tract infection	15 (8.6)	3 (2.9)	3 (1.7)	0

continued

In Studies 1, 2 and 4 with SC administration of VIDAZA, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of VIDAZA. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Overall, adverse reactions were qualitatively similar between the IV and SC studies. Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (e.g. erythema or pain) and catheter site reactions (e.g. infection, erythema, or hemorrhage).

In clinical studies of either SC or IV VIDAZA, the following serious adverse reactions occurring at a rate of < 5% (and not described in Tables 1 or 2) were reported:

Blood and lymphatic system disorders: agranulocytosis, bone marrow failure, pancytopenia, splenomegaly.

Cardiac disorders: atrial fibrillation, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, congestive cardiomyopathy.

Eye disorders: eye hemorrhage.

Gastrointestinal disorders: diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.

General disorders and administration site conditions: catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.

Hepatobiliary disorders: cholecystitis.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: abscess limb, bacterial infection, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.

Metabolism and nutrition disorders: dehydration.

Musculoskeletal and connective tissue disorders: bone pain aggravated, muscle weakness, neck pain.

Neoplasms benign, malignant and unspecified: leukemia cutis.

Nervous system disorders: cerebral hemorrhage, convulsions, intracranial hemorrhage.

Renal and urinary disorders: loin pain, renal failure.

Respiratory, thoracic and mediastinal disorders: hemoptysis, lung infiltration, pneumonitis, respiratory distress.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, rash pruritic, skin induration.

Surgical and medical procedures: cholecystectomy.

Vascular disorders: orthostatic hypotension.

6.3 Postmarketing Experience

Adverse reactions identified from spontaneous reports have been similar to those reported during clinical trials with VIDAZA.

7 DRUG INTERACTIONS

No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine was teratogenic in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Female partners of male patients receiving VIDAZA should not become pregnant [see *Nonclinical Toxicology* (13)].

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m² (approximately 8% of the recommended human daily dose on a mg/m² basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3-12 mg/m² (approximately 4%-16% the recommended human daily dose on a mg/m² basis).

In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 (postimplantation) at a dose of 6 mg/m² (approximately 8% of the recommended human daily dose on a mg/m² basis), although treatment in the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m² (approximately 8% the recommended human daily dose on a mg/m² basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3-12 mg/m² on gestation days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastrochisis, edema, and rib abnormalities).

8.3 Nursing Mothers

It is not known whether azacitidine or its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients < 65 years of age and patients 65 years of age and older.

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function [see *Dosage and Administration* (2.5) and *Warnings and Precautions* (5.3)].

8.6 Gender

There were no clinically relevant differences in safety and efficacy based on gender.

8.7 Race

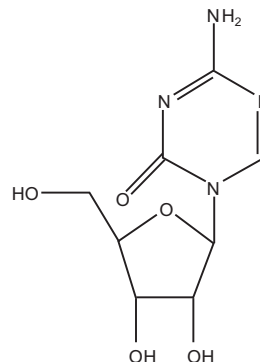
Greater than 90% of all patients in all trials were Caucasian. Therefore, no comparisons between Caucasians and non-Caucasians were possible.

10 OVERDOSAGE

One case of overdose with VIDAZA was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m², almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day. In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for VIDAZA overdose.

11 DESCRIPTION

VIDAZA (azacitidine for injection) contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:



The empirical formula is C₈H₁₂N₄O₅. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of VIDAZA contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIDAZA is a pyrimidine nucleoside analog of cytidine. VIDAZA is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

12.3 Pharmacokinetics

The pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m² subcutaneous (SC) dose and a single 75 mg/m² intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following SC administration of ¹⁴C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

Special Populations

The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied [see *Dosage and Administration* (2.4), *Contraindications* (4.1) and *Warnings and Precautions* (5.2, 5.3)].

Drug-Drug Interactions

Drug interaction studies with azacitidine have not been conducted.

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolized by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.

The potential of azacitidine to inhibit cytochrome P450 (CYP) enzymes is not known.

In vitro studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 μM to 100 μM does not induce CYP 1A2, 2C19, or 3A4/5.

13 NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m², approximately 8% the recommended human daily dose on a mg/m² basis) administered IP three times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/m², approximately 8% the recommended human daily dose on a mg/m² basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m² (approximately 20-80% the recommended human daily dose on a mg/m² basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in in vitro bacterial systems *Salmonella typhimurium* strains TA100 and several strains of trpE8, *Escherichia coli* strains WP14 Pro, WP3103P, WP3104P, and CC103; in in vitro forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an in vitro micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/m² (approximately 9% the recommended human daily dose on a mg/m² basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15-30 mg/m² (approximately 20-40% the recommended human daily dose on a mg/m² basis) resulted in decreased weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m² resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation.

14 CLINICAL STUDIES

Myelodysplastic Syndromes (MDS)

Study 1 was a randomized, open-label, controlled trial carried out in 53 U.S. sites compared the safety and efficacy of subcutaneous VIDAZA plus supportive care with supportive care alone ("observation") in patients with any of the five FAB subtypes of myelodysplastic syndromes (MDS): refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). RA and RARS patients were included if they met one or more of the following criteria: required packed RBC transfusions; had platelet counts $\leq 50.0 \times 10^9/L$; required platelet transfusions; or were neutropenic (ANC $< 1.0 \times 10^9/L$) with infections requiring treatment with antibiotics. Patients with acute myelogenous leukemia (AML) were not intended to be included. Supportive care allowed in this study included blood transfusion products, antibiotics, antiemetics, analgesics and antipyretics. The use of hematopoietic growth factors was prohibited. Baseline patient and disease characteristics are summarized in Table 3; the 2 groups were similar.

VIDAZA was administered at a subcutaneous dose of 75 mg/m² daily for 7 days every 4 weeks. The dose was increased to 100 mg/m² if no beneficial effect was seen after 2 treatment cycles. The dose was decreased and/or delayed based on hematologic response or evidence of renal toxicity. Patients in the observation arm were allowed by protocol to cross over to VIDAZA if they had increases in bone marrow blasts, decreases in hemoglobin, increases in red cell transfusion requirements, or decreases in platelets, or if they required a platelet transfusion or developed a clinical infection requiring treatment with antibiotics. For purposes of assessing efficacy, the primary endpoint was response rate (as defined in Table 4).

Of the 191 patients included in the study, independent review (adjudicated diagnosis) found that 19 had the diagnosis of AML at baseline. These patients were excluded from the primary analysis of response rate, although they were included in an intent-to-treat (ITT) analysis of all patients randomized. Approximately 55% of the patients randomized to observation crossed over to receive VIDAZA treatment.

Table 3. Baseline Demographics and Disease Characteristics

	VIDAZA (N=99)	Observation (N=92)
Gender (n%)		
Male	72 (72.7)	60 (65.2)
Female	27 (27.3)	32 (34.8)
Race (n%)		
White	93 (93.9)	85 (92.4)
Black	1 (1.0)	1 (1.1)
Hispanic	3 (3.0)	5 (5.4)
Asian/Oriental	2 (2.0)	1 (1.1)
Age (years)		
N	99	91
Mean \pm SD	67.3 \pm 10.39	68.0 \pm 10.23
Range	31 - 92	35 - 88

continued

Table 3. Baseline Demographics and Disease Characteristics

	VIDAZA (N=99)	Observation (N=92)
Adjudicated MDS diagnosis at study entry (n%)		
RA	21 (21.2)	18 (19.6)
RARS	6 (6.1)	5 (5.4)
RAEB	38 (38.4)	39 (42.4)
RAEB-T	16 (16.2)	14 (15.2)
CMML	8 (8.1)	7 (7.6)
AML	10 (10.1)	9 (9.8)
Transfusion product used in 3 months before study entry (n%)		
Any transfusion product	70 (70.7)	59 (64.1)
Blood cells, packed human	66 (66.7)	55 (59.8)
Platelets, human blood	15 (15.2)	12 (13.0)
Hetastarch	0 (0.0)	1 (1.1)
Plasma protein fraction	1 (1.0)	0 (0.0)
Other	2 (2.0)	2 (2.2)

Table 4. Response Criteria

		RA	RARS	RAEB	RAEB-T	CMML
Complete Response (CR), duration \geq 4 weeks	Marrow	<5% blasts				
	Peripheral Blood	Normal CBC if abnormal at baseline Absence of blasts in the peripheral circulation				
Partial Response (PR), duration \geq 4 weeks	Marrow	No marrow requirements	\geq 50% decrease in blasts Improvement of marrow dyspoiesis			
	Peripheral Blood	\geq 50% restoration in the deficit from normal levels of baseline white cells, hemoglobin and platelets if abnormal at baseline No blasts in the peripheral circulation For CMML, if WBC is elevated at baseline, a \geq 75% reduction in the excess count over the upper limit of normal				

The overall response rate (CR + PR) of 15.7% in VIDAZA-treated patients without AML (16.2% for all VIDAZA randomized patients including AML) was statistically significantly higher than the response rate of 0% in the observation group ($p < 0.0001$) (Table 5). The majority of patients who achieved either CR or PR had either 2 or 3 cell line abnormalities at baseline (79%; 11/14) and had elevated bone marrow blasts or were transfusion dependent at baseline. Patients responding to VIDAZA had a decrease in bone marrow blasts percentage, or an increase in platelets, hemoglobin or WBC. Greater than 90% of the responders initially demonstrated these changes by the 5th treatment cycle. All patients who had been transfusion dependent became transfusion independent during PR or CR. The mean and median duration of clinical response of PR or better was estimated as 512 and 330 days, respectively; 75% of the responding patients were still in PR or better at completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML.

Table 5. Response Rates

	VIDAZA (N=89)	Observation Before Crossover (N=83)	P value
Response	n (%)	n (%)	
Overall (CR+PR)	14 (15.7)	0 (0.0)	(<0.0001)
Complete (CR)	5 (5.6)	0 (0.0)	(0.06)
Partial (PR)	9 (10.1)	0 (0.0)	--

Patients in the observation group who crossed over to receive VIDAZA treatment (47 patients) had a response rate of 12.8%.

Study 2, a multi-center, open-label, single-arm study of 72 patients with RAEB, RAEB-T, CMML, or AML was also carried out. Treatment with subcutaneous VIDAZA resulted in a response rate (CR + PR) of 13.9%, using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 810 and 430 days, respectively; 80% of the responding patients were still in PR or better at the time of completion of study involvement. In Study 3, another open-label, single-arm study of 48 patients with RAEB, RAEB-T, or AML, treatment with intravenous VIDAZA resulted in a response rate of 18.8%, again using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 389 and 281 days, respectively; 67% of the responding patients were still in PR or better at the time of completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML in both of these studies.

VIDAZA dosage regimens in these 2 studies were similar to the regimen used in the controlled study.

Benefit was seen in patients who did not meet the criteria for PR or better, but were considered "improved." About 24% of VIDAZA-treated patients were considered improved, and about 2/3 of those lost transfusion dependence. In the observation group, only 5/83 patients met criteria for improvement; none lost transfusion dependence. In all 3 studies, about 19% of patients met criteria for improvement with a median duration of 195 days.

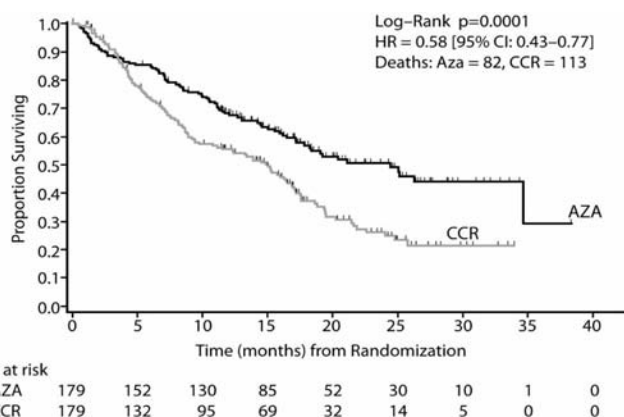
Study 4 was an international, multicenter, open-label, randomized trial in MDS patients with RAEB, RAEB-T or modified CMMoL according to FAB classification and Intermediate-2 and High risk according to IPSS classification. Of the 358 patients enrolled in the study, 179 were randomized to receive azacitidine plus best supportive care (BSC) and 179 were randomized to receive conventional care regimens (CCR) plus BSC (105 to BSC alone, 49 to low dose cytarabine and 25 to chemotherapy with cytarabine and anthracycline). The primary efficacy endpoint was overall survival.

The azacitidine and CCR groups were comparable for baseline parameters. The median age of patients was 69 years (range was 38-88 years), 98% were Caucasian, and 70% were male. At baseline, 95% of the patients were higher risk by FAB classification: RAEB (58%), RAEB-T (34%), and CMMoL (3%). By IPSS classification, 87% were higher risk: Int-2 (41%), High (47%). At baseline, 32% of patients met WHO criteria for AML.

Azacitidine was administered subcutaneously at a dose of 75 mg/m² daily for 7 consecutive days every 28 days (which constituted one cycle of therapy). Patients continued treatment until disease progression, relapse after response, or unacceptable toxicity. Azacitidine patients were treated for a median of 9 cycles (range 1 to 39), BSC only patients for a median of 7 cycles (range 1 to 26), low dose cytarabine patients for a median of 4.5 cycles (range 1 to 15), and chemotherapy with cytarabine and anthracycline patients for a median of 1 cycle (range 1 to 3, i.e. induction plus 1 or 2 consolidation cycles).

In the Intent-to-Treat analysis, patients treated with azacitidine demonstrated a statistically significant difference in overall survival as compared to patients treated with CCR (median survival of 24.5 months vs. 15.0 months; stratified log-rank p=0.0001). The hazard ratio describing this treatment effect was 0.58 (95% CI: 0.43, 0.77).

Kaplan-Meier Curve of Time to Death from Any Cause: (Intent-to-Treat Population)



Key: AZA = azacitidine; CCR = conventional care regimens; CI = confidence interval; HR = Hazard Ratio

Azacitidine treatment led to a reduced need for red blood cell transfusions (see Table 6). In patients treated with azacitidine who were RBC transfusion dependent at baseline and became transfusion independent, the median duration of RBC transfusion independence was 13.0 months.

Table 6. Effect of Azacitidine on RBC Transfusions in MDS Patients

Efficacy Parameter	Azacitidine plus BSC (n=179)	Conventional Care Regimens (n=179)
Number and percent of patients who were transfusion dependent at baseline who became transfusion independent on treatment ¹	50/111 (45.0%) (95% CI: 35.6%, 54.8%)	13/114 (11.4%) (95% CI: 6.2%, 18.7%)
Number and percent of patients who were transfusion-independent at baseline who became transfusion-dependent on treatment	10/68 (14.7%) (95% CI: 7.3%, 25.4%)	28/65 (43.1%) (95% CI: 30.9%, 56.0%)

¹ A patient was considered RBC transfusion independent during the treatment period if the patient had no RBC transfusions during any 56 consecutive days or more during the treatment period. Otherwise, the patient was considered transfusion dependent.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VIDAZA (azacitidine for injection) is supplied as a lyophilized powder in 100 mg single-use vials packaged in cartons of 1 vial (NDC 59572-102-01).

Storage

Store unconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) (See USP Controlled Room Temperature).

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be applied. Several guidelines on this subject have been published.¹⁻⁴ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their physician about any underlying liver or renal disease.

Advise women of childbearing potential to avoid becoming pregnant while receiving treatment with VIDAZA. For nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Advise men not to father a child while receiving treatment with VIDAZA.

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Summit, NJ 07901

Manufactured by: Ben Venue Laboratories, Inc.
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Or
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