

PRODUCT MONOGRAPH

Pr **ISTODAX**[®]

romidepsin for injection

Lyophilized powder for injection
10mg/vial

Antineoplastic Agent
Histone Deacetylase (HDAC) Inhibitor

ISTODAX[®] (romidepsin), indicated for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

**For further information for ISTODAX[®] please refer to Health Canada's Notice of Compliance with conditions – drug products website:
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>**

Celgene Inc.
6755 Mississauga Road
Suite 600
Mississauga, ON
L5N 7Y2

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**This product has been approved under the
Notice of Compliance with Conditions (NOC/c)
policy for one or all of its indicated uses.**

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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Pr **ISTODAX**[®]

Romidepsin for injection

PART I: HEALTH PROFESSIONAL INFORMATION

ISTODAX[®] (romidepsin), indicated for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder for solution, 10 mg romidepsin per vial	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

NOC/c INDICATIONS AND CLINICAL USE

ISTODAX[®] (romidepsin for injection) is indicated for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy.

Approval is based on response rates demonstrated in a single-arm trial (see **CLINICAL TRIALS**). Improvement in overall survival has not been demonstrated with ISTODAX.

Geriatrics (> 65 years of age):

No overall differences in safety or effectiveness were observed between the elderly (> 65 years) and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age):

The safety and effectiveness of ISTODAX in pediatric patients has not been established.

NOC/c **CONTRAINDICATIONS**

- Patients who are hypersensitive to romidepsin or to any ingredient in the formulation. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

NOC/c **WARNINGS AND PRECAUTIONS**

Serious Warnings and Precautions

ISTODAX[®] (romidepsin for injection) should be administered under the supervision of a physician experienced with the use of chemotherapy and with treatment of peripheral T-cell lymphoma.

- Pancytopenia (see **Warnings and Precautions**)
- QT interval prolongation (see **Warnings and Precautions**)
- Fatal infections (see **Warnings and Precautions**)
- Tumor lysis syndrome (see **Warnings and Precautions**)
- Potential fetal harm (see **Warnings and Precautions, Toxicology**)

ISTODAX has not been studied in patients with hepatic or renal impairment.

General

Asthenia/fatigue were commonly reported in clinical trials with ISTODAX but were generally mild to moderate in intensity. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks (see **ADVERSE REACTIONS and DRUG INTERACTIONS, Drug-Lifestyle Interactions**).

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with romidepsin (see **TOXICOLOGY**).

Cardiovascular

QTc Prolongation and Electrocardiographic Changes: ISTODAX has been associated with QTc interval prolongation (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering ISTODAX to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., eating disorders); bradycardia (<50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

QTc prolongation as well as several morphological changes in ECGs (including T wave and ST-segment changes) have been reported in clinical studies. Many of the ECG morphologic abnormalities were also observed at baseline. These ECG changes were transient and were not associated with functional cardiovascular changes or with symptoms. The clinical significance of these changes is unknown.

In view of potential ECG changes, an ECG should be performed at baseline in all patients. Serum potassium and magnesium should be within the normal range before each administration of ISTODAX.

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, appropriate cardiovascular monitoring precautions should be considered, such as the monitoring of ECGs and electrolytes at baseline and periodically during treatment (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; DRUG INTERACTIONS**).

Heart Rate: ISTODAX is associated with an increase in heart rate (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). Caution should be observed in patients with a history of ischemic heart disease or tachyarrhythmias.

General: Patients with a significant cardiac history have been excluded from the clinical trials. Hence, safety data for subjects with significant cardiac history is not available.

Drug Interactions

Coumarin-Derivative Anticoagulants

Physicians should carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX and coumarin-derivatives (see **DRUG INTERACTIONS, Drug-Drug-Interactions**).

Estrogen-Containing Contraceptives

Females of childbearing potential should be advised that ISTODAX may reduce the effectiveness of estrogen-containing contraceptives (see **DRUG INTERACTIONS, Drug-Drug-Interactions**).

Gastrointestinal

Gastrointestinal reactions, such as nausea, vomiting, constipation and diarrhea were commonly reported but generally mild to moderate in intensity and non serious, and most patients continued ISTODAX despite the occurrence of GI events. Dehydration concurrent with vomiting and/or diarrhea was uncommon. Antiemetic use is recommended and was commonly given in clinical trials.

Hematologic

Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), anemia and febrile neutropenia. The frequency of Grade 3 or 4 cytopenias among the 131 patients in the pivotal PTCL trial were 24%, 6%, 11% and 3%, respectively. These hematological parameters should therefore be monitored during treatment with ISTODAX, and the dose should be modified, as necessary (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS** and **Monitoring and Laboratory Tests**).

Hepatic

In the pivotal PTCL clinical trial Grade 3 elevated aspartate aminotransferase (AST) occurred in 1 (<1%) patient. There were no Grade 3 or 4 elevations of alanine aminotransferase (ALT) or gamma-glutamyltransferase. No dedicated hepatic impairment study has been conducted for ISTODAX. Patients with moderate and severe hepatic impairment should be treated with caution (see **DOSAGE AND ADMINISTRATION**).

Infection

Serious and sometimes fatal infections, including pneumonia, sepsis, opportunistic infections including pneumocystis jiroveci pneumonia (PJP) and viral reactivation including Epstein Barr, hepatitis B viruses, and cytomegalovirus (CMV), have been reported in clinical trials with ISTODAX. These can occur during treatment and within 30 days after treatment, and the risk may be higher in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow. The observed rate of infections in patients with PTCL was 57%, and the most commonly reported types were upper respiratory tract infection (9%), urinary tract infection (7%), pneumonia (7%), oral

candidiasis (6%) and sepsis and nasopharyngitis (5%). Grade ≥ 3 infections occurred in 20% of patients with PTCL, which may be explained by disease-specific risks such as bone marrow involvement and a prior history of chemotherapy and/or bone marrow transplantation.

Reactivation of hepatitis B, cytomegalovirus and Epstein-Barr virus infections has been reported. Monitoring or prophylaxis should be considered.

Reactivation of Epstein Barr viral infection leading to liver failure, and in one case death, has occurred in a trial of patients with relapsed or refractory extranodal NK/T-cell lymphoma (not an approved indication).

Renal

No dedicated renal impairment study has been conducted for ISTODAX. Based upon the population pharmacokinetic analysis, renal impairment is not expected to significantly influence drug exposure (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). Use of ISTODAX in patients with end-stage renal disease has not been evaluated and these patients should therefore be treated with caution.

Sensitivity/Resistance

Hypotension and other symptoms possibly representing hypersensitivity to the compound have been observed uncommonly during the infusion of ISTODAX.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden should be closely monitored, appropriate precautions should be taken, and treatment should be instituted as appropriate.

Sexual Function/Reproduction

Romidepsin may impair male and female fertility. Animal studies have shown morphological changes in the testes and mammary glands (males) and ovaries, uterus, vagina and mammary glands (females) after repeated dosing in rats and dogs at below clinical exposures (see **TOXICOLOGY**). These changes may be irreversible. Patients should be advised that their sexual function/reproduction may be compromised by the treatment with ISTODAX.

Special Populations

Pregnant Females: ISTODAX should not be used during pregnancy. Based on its mechanism of action, ISTODAX may cause fetal harm when administered to a pregnant woman. In pregnant rats, romidepsin was embryocidal and teratogenic at doses/exposures lower than in humans. Drug-related fetal effects included rotated limbs, folded retina, interrupted aortic arch, and increased incidence of supernumerary thoracic ribs (see **TOXICOLOGY**).

ISTODAX may reduce the effectiveness of estrogen-containing contraceptives (see **DRUG INTERACTIONS**).

Females of Childbearing Potential: Females of childbearing potential must be apprised of the potential hazard to the fetus which includes potential birth defects and fetal death (embryotoxicity).

Due to the potential hazard to the fetus, females of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ISTODAX. Adequate contraception should be used while receiving ISTODAX and up to 8 weeks after ending treatment. Because ISTODAX may reduce the effectiveness of estrogen-containing contraceptives, alternative methods should be used (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Non-clinical findings suggest that ISTODAX can bind to the estrogen receptor and thus may modulate estrogen signaling (see **TOXICOLOGY**). It is not known if romidepsin has any estrogenic or anti-estrogenic effects.

Nursing Females: It is not known whether romidepsin is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving romidepsin.

Male Patients: It is not known if romidepsin is present in semen. Male patients must take appropriate precautions to avoid fathering a child during ISTODAX treatment. Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners while being treated with ISTODAX.

Based on in-animal studies romidepsin has a potential to affect sexual function and fertility (see **TOXICOLOGY**). Semen preservation prior to initiation of ISTODAX therapy could be considered.

Pediatrics (< 18 years of age): The safety and effectiveness of ISTODAX in pediatric patients has not been established.

Geriatrics (> 65 years of age): In GPI-06-0002, 38% of patients were > 65 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

Vascular Disorders

In the pivotal PTCL trial 4 patients (3%) and 2 patients (2%) experienced Grade 3 or 4 deep vein thrombosis or hypotension, respectively (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Monitoring and Laboratory Tests

Hematological

Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; therefore, these hematological parameters should be monitored during treatment with ISTODAX, at a minimum, prior to each treatment cycle, and the dose should be modified, as necessary (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**).

Biochemical

In view of potential ECG changes, potassium and magnesium should be within the normal range before administration of ISTODAX. Carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX and coumarin derivatives.

Cardiac Toxicities

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, appropriate cardiovascular monitoring precautions should be considered, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment (see **WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS; ACTIONS AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of ISTODAX (romidepsin for injection) was evaluated in 131 patients with PTCL in a single arm clinical study (GPI-06-0002) in which patients received a starting dose of 14 mg/m². The mean duration of treatment and number of doses were 5.6 months and 15.5 doses, respectively, corresponding to ~6 cycles.

Common Adverse Reactions: Overall, the most common adverse events reported were functional gastrointestinal (GI) disorders (82%), including reports of nausea with or without vomiting (64%), diarrhea (36%) and constipation (30%); hematological disorders (57%), including thrombocytopenia (41%), neutropenia (30%), and anemia (24%); asthenic conditions (55%), including reports of fatigue (41%) and asthenia (16%); infections (55%); pyrexia (35%); anorexia (28%); and dysgeusia (21%).

Serious Adverse Reactions: Infections were the most common type of SAE reported, with 26 patients (20%) experiencing a serious infection during Study GPI-06-0002. Serious adverse reactions reported in ≥ 2% of patients in Study GPI-06-0002 were pyrexia (8%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis (4%), febrile neutropenia, gastrointestinal and abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnea, and dehydration (2%).

Opportunistic infections including viral reactivation have been reported in PTCL patients (see WARNINGS AND PRECAUTIONS, Infection).

In Study GPI-06-0002, deaths within 30 days of the last dose occurred in 8 patients (6%), most frequently due to disease progression. There were 5 deaths due to infections in the setting of disease progression concurrent with multi-organ failure/sepsis, pneumonia, septic shock, candida sepsis, and sepsis/cardiogenic shock.

Dose Modifications and Discontinuations

Among the 131 patients with PTCL in the pivotal study, 63 (48%) required at least 1 dose to be held and 14 (11%) required at least 1 dose reduction for the management of an adverse event. Doses were most commonly held for the management of thrombocytopenia (23 patients, 18%) and neutropenia (15 patients; 11%). Other events requiring a dose to be held in >2 patients included asthenia, diarrhea, fatigue, pneumonia, pyrexia, and upper respiratory tract infection (3 patients each; 2%). The only adverse event requiring a dose reduction for >2 patients was thrombocytopenia (4 patients; 3%).

Adverse events leading to discontinuation were reported in 25 (19%) of the 131 patients. The most common events leading to discontinuation were thrombocytopenia and pneumonia (each 3 patients, 2%) and fatigue, sepsis, and dyspnea (each 2 patients, 2%). All other events leading to discontinuation were reported in 1 patient each.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The principal clinically important groups of adverse reactions to be expected in patients treated with romidepsin are gastrointestinal disturbances, asthenic conditions, infections, hematological toxicities and clinical chemistry abnormalities.

Table 1 below contains the adverse reactions from Study GPI-06-0002 using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0) for which a causal relationship with ISTODAX treatment could reasonably be established.

Table 1: Adverse Drug Reactions Occurring in $\geq 5\%$ of Patients with PTCL in Study GPI-06-0002 (N=131)

Adverse Reactions	Study GPI-06-0002	
	All	Grade 3 or 4
<i>Any adverse reactions</i>	128 (97)	88 (67)
Gastrointestinal disorders		
Nausea	77 (59)	3 (2)
Vomiting	51 (39)	6 (5)
Diarrhea	47 (36)	3 (2)
Constipation	39 (30)	1 (<1)
Abdominal pain	18 (14)	3 (2)
Stomatitis	14 (11)	0
Dyspepsia	11 (8)	0
Abdominal pain upper	9 (7)	1 (<1)
General disorders and administration site conditions		
Asthenia/Fatigue ^a	72 (55)	11 (8)
Pyrexia	47 (36)	8 (6)
Chills	14 (11)	1 (<1)
Edema peripheral	13 (10)	1 (<1)
Chest pain	10 (8)	4 (3)
Pain	10 (8)	1 (<1)
Blood and lymphatic system disorders		
Thrombocytopenia	53 (41)	32 (24)
Neutropenia	39 (30)	26 (20)
Anemia	33 (25)	14 (11)
Leukopenia	16 (12)	8 (6)
Metabolism and nutrition disorders		
Anorexia	37 (28)	2 (2)
Hypokalemia	14 (11)	3 (2)
Decreased appetite	12 (9)	1 (<1)
Hypomagnesemia	9 (7)	0
Nervous system disorders		
Dysgeusia	27 (21)	0
Headache	19 (15)	0
Dizziness	11 (8)	0
Lethargy	8 (6)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Cough	23 (18)	0
Dyspnea	17 (13)	3 (2)
Oropharyngeal pain	8 (6)	0
Rhinorrhea	8 (6)	0
Investigations		
Weight decreased	14(11)	0
Cardiac disorders		
Tachycardia	13 (10)	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	12 (9)	0
Myalgia	8 (6)	1 (<1)
Back pain	9 (7)	1 (<1)
Pain in extremity	7 (5)	0
Arthralgia	7 (5)	2 (2)

Table 1: Adverse Drug Reactions Occurring in $\geq 5\%$ of Patients with PTCL in Study GPI-06-0002 (N=131) (Continued)

Infections and infestations		
Upper respiratory tract infection	12 (9)	2 (2)
Urinary tract infection	9 (7)	1 (<1)
Pneumonia	9 (7)	7 (5)
Oral candidiasis	8 (6)	1 (<1)
Sepsis	7 (5)	7 (5)
Cellulitis	6 (5)	5 (4)
Nasopharyngitis	7 (5)	0
Skin and subcutaneous tissue disorders		
Pruritus	12 (9)	0
Skin lesion	11 (8)	0
Rash	10 (8)	1 (<1)
Night sweats	9 (7)	0
Dry skin	8 (6)	0
Vascular disorders		
Hypotension	11 (8)	2 (2)
Psychiatric disorders		
Anxiety	9 (7)	0
Insomnia	9 (7)	0
Depression	6 (5)	0

^a Combined MedDRA Preferred Terms (PT's), High Level Terms (HLT's) or System Organ Class (SOC) Terms are presented instead of individual MedDRA PT's to provide a more accurate representation of similar types of adverse drug reactions

Abnormal Hematologic and Clinical Chemistry Findings

A summary of the proportion of patients who had shifts from baseline to a higher value on study based on CTCAE are summarized in [Table 2](#) for both hematology and chemistry parameters.

Table 2: Shifts from Baseline to Worst Value on Study by CTC Grade

Laboratory Parameter	Study GPI-06-0002	
	All Shifts ¹ n/N (%)	Grade 3 or 4 ² n/N (%)
Hematology		
Hemoglobin decreased	81/129 (63)	13/129 (10)
Platelets decreased	103/129 (80)	37/129 (29)
Lymphocytes decreased	78/129 (61)	53/129 (41)
WBC decreased	72/129 (56)	16/129 (12)
Neutrophils decreased	59/129 (46)	26/129 (20)
Clinical chemistry		
Sodium increased	10/129 (8)	2/129 (2)
Sodium decreased	33/129 (26)	8/129 (6)
Potassium increased	26/129 (20)	3/129 (2)
Potassium decreased	28/129 (22)	4/129 (3)
Calcium increased	10/129 (8)	1/129 (<1)
Calcium decreased	51/129 (40)	3/129 (2)
Magnesium increased	49/129 (38)	28/129 (22)
Magnesium decreased	24/129 (19)	0
Creatinine increased	21/129 (16)	0
AST increased	30/127 (24)	3/127 (2)
ALT increased	36/124 (29)	3/124 (2)
Alkaline phosphatase increased	24/128 (19)	0
Albumin decreased	42/125 (34)	3/125 (2)
Bilirubin increased	11/128 (9)	0

- 1 Any shift from baseline to worst value on study (i.e., includes shifts from Grade 0 at baseline to Grade 1 on treatment)
- 2 Any shift from baseline to worst value of Grade 3 or 4 on study (i.e., includes shifts from Grade 3 at baseline to Grade 4 on treatment)

Post-Market Adverse Drug Reactions

Infections and Infestations: Viral reactivation (EBV, including a fatal case, hepatitis B and CMV viruses) was reported from clinical trials in the postmarketing setting.

DRUG INTERACTIONS

Cytochrome P450 3A4 Enzymes

Romidepsin is metabolized by CYP3A4. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme.

CYP3A4 Inhibitor: Strong CYP3A4 inhibitors increase concentrations of romidepsin. In a pharmacokinetic drug interaction trial the strong CYP3A4 inhibitor ketoconazole increased romidepsin (AUC_{∞}) by approximately 25%. Monitor for toxicity related to increased romidepsin exposure when romidepsin is co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).

CYP3A4 Inducer: Avoid co-administration of ISTODAX with rifampin. In a pharmacokinetic drug interaction trial with co-administered rifampin (a strong CYP3A4 inducer), romidepsin exposure was increased by approximately 80% and 60% for AUC_∞ and C_{max}, respectively. Typically, co-administration of CYP3A4 inducers decrease concentrations of drugs metabolized by CYP3A4. The increase in exposure seen after co-administration with rifampin is likely due to rifampin's inhibition of an undetermined hepatic uptake process limiting romidepsin access to induced CYP3A4. It is unknown if other strong CYP3A4 inducers (e.g., dexamethasone, carbamazepine, phenytoin, rifabutin, rifapentine, phenobarbital, St. John's Wort) would alter the exposure of ISTODAX. Therefore, avoid the concomitant administration of ISTODAX with strong CYP3A4 inducers.

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Reference	Effect	Clinical comment
Coumarin derivatives	CT	Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin.	Although the interaction potential between ISTODAX and coumarin derivatives has not been formally studied, physicians should carefully monitor PT and INR in patients concurrently administered ISTODAX and coumarin derivatives.
Estrogen-containing contraceptives	T	An <i>in vitro</i> binding assay determined that romidepsin competes with β-estradiol for binding to estrogen receptors.	Females of childbearing potential should be advised that ISTODAX may reduce the effectiveness of estrogen-containing contraceptives (see WARNINGS AND PRECAUTIONS, Pregnant Females). Therefore, alternative methods of non-estrogen-containing contraception (e.g. condoms, intrauterine device) should be used in patients receiving ISTODAX. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.
Drugs that inhibit drug transport systems	T	Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1).	If ISTODAX is administered with drugs that inhibit P-gp, increased concentrations of romidepsin are likely, and caution should be exercised.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Other QT/QTc-Prolonging Drugs: Caution should be observed if ISTODAX is administered with drugs that cause QTc prolongation. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone);

- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone);
- antidepressants (SSRI/SNRI e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- domperidone;
- 5-HT₃ receptor antagonists (e.g., dolasetron, ondansetron);
- tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Can Decrease Electrolyte Levels: Avoid when possible the concomitant use of drugs that can disrupt electrolyte levels during treatment with ISTODAX. Drugs that can impact electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics;
- laxatives and enemas;
- amphotericin B;
- high dose corticosteroids

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established (see **WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Patients should refrain from taking St. John's Wort.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies of the effects of ISTODAX on the ability to drive or operate machines have been performed. However, treatment with ISTODAX is commonly associated with asthenia and fatigue which can be severe (see **ADVERSE REACTIONS**). If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks.

NOC/c **DOSAGE AND ADMINISTRATION**

Romidepsin treatment should only be administered under the supervision of a physician qualified in the use of chemotherapeutic agents and administration should be confined to units specialized in the use of cytotoxic chemotherapy.

Dosing Considerations

- ISTODAX (romidepsin for injection) is moderately emetogenic. Antiemetics were commonly used in clinical trials involving ISTODAX. Premedication with antiemetics is recommended.
- Serum potassium and magnesium should be within the normal range before each administration of ISTODAX.
- ISTODAX is intended for intravenous infusion only after reconstitution with the supplied diluent and after further dilution with 0.9% Sodium Chloride, USP.
- ISTODAX has not been studied in patients with moderately or severely impaired hepatic function or end stage renal function.
- Dosage given should be adjusted according to tolerability as described below.

Recommended Dose and Dosage Adjustment

The recommended dose is 14 mg/m² administered intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the therapy.

Dose Modifications

Nonhematologic toxicities except alopecia

- Grade 2 or 3 toxicity: Treatment with ISTODAX should be delayed until toxicity returns to ≤ Grade 1 or baseline, then therapy may be restarted at 14 mg/m². If Grade 3 toxicity recurs, treatment with ISTODAX should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m².
- Grade 4 toxicity: Treatment with ISTODAX should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m².

- ISTODAX should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with ISTODAX should be delayed until the specific cytopenia returns to ANC $\geq 1.5 \times 10^9/L$ and/or platelet count $\geq 75 \times 10^9/L$ or baseline, then therapy may be restarted at 14 mg/m².
- Grade 4 febrile ($\geq 38.5^\circ C$) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with ISTODAX should be delayed until the specific cytopenia returns to \leq Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m².

Pediatrics

The safety and effectiveness of ISTODAX has not been evaluated in pediatric patients (age <18).

Geriatrics

The safety and effectiveness of ISTODAX has not been evaluated in elderly patients (age >65). Elderly patients may experience greater sensitivity to treatments with ISTODAX and may require dose modifications.

Hepatic Impairment

No dedicated studies with ISTODAX in patients with impaired hepatic function have been carried out therefore there is no available data regarding recommendations for dose adjustment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Renal Impairment

No dedicated studies with ISTODAX in patients with impaired renal function have been carried out therefore there is no available data regarding recommendations for dose adjustment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

Missed Dose

If a dose is missed, it should be administered as soon as possible unless it is within 5 days of the next scheduled dose, in which case dosing should be resumed as scheduled.

Reconstitution and Administration

ISTODAX (romidepsin for injection) should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

ISTODAX must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

Strength	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
10 mg/ vial	2.2 mL of the supplied diluent	2 mL	5 mg/mL

- Each 10 mg single-use vial of ISTODAX which contains 11 mg of romidepsin must be reconstituted with 2.2 mL of the supplied diluent (vial contains 2.4 mL of diluent). The final reconstituted 10 mg single-use vial contains 2.2 mL solution of ISTODAX, which includes a 0.2 mL overfill. With a suitable syringe, aseptically withdraw 2.2 mL from the supplied diluent vial, and slowly inject it into the ISTODAX for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain ISTODAX 5 mg/mL.
- Extract the appropriate amount of ISTODAX from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute ISTODAX in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

Stability and Compatibility

ISTODAX should be prepared immediately before use and the reconstituted and diluted solution should be administered as soon as possible. The reconstituted ISTODAX solution is chemically stable for up to 8 hours at room temperature. The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles, and is chemically stable for up to 24 hours when stored at room temperature. However, it should be administered as soon after dilution as possible.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No specific information is available on the treatment of overdose of ISTODAX (romidepsin for injection). Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2 fold the recommended human dose based on the body surface area, included irregular respiration, irregular heartbeats, staggering gait, tremor, and tonic convulsions (see **TOXICOLOGY**). In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required.

There is no known antidote for romidepsin and it is not known if romidepsin is dialyzable.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Romidepsin is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. In vitro, romidepsin causes the accumulation of acetylated histones and induces cell cycle arrest and apoptosis of some cancer cell lines. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

Cardiac Electrophysiology

The potential effect of romidepsin on the QTcF interval was evaluated in 26 patients with advanced malignancies given romidepsin at doses of 14 mg/m² as a 4-hour intravenous infusion, and at doses of 8, 10 or 12 mg/m² as a 1-hour infusion.

QTcF (QTcF=QT/[RR/1000]^{0.33}) increases were also observed with a maximum mean increase of 10.7 ms at the 2 h time point after the start of romidepsin infusion. At 24 hours after the start of romidepsin infusion, the mean increase in the QTc interval was 5.5 ms. Interpretation of the QTcF interval data is confounded by the use of QTc-prolonging antiemetic premedications in most of the subjects (See **WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; DRUG INTERACTIONS**).

Romidepsin was associated with a delayed concentration-dependent increase in heart rate in patients with advanced cancer with a maximum mean increase in heart rate of 18.2 bpm occurring at the 6 hour time point after start of romidepsin infusion for patients receiving 14 mg/m² as a 4-hour infusion. At 24 hours after the start of romidepsin infusion, the mean increase in heart rate was 1.4 bpm.

Pharmacokinetics

Table 4: Summary of romidepsin pharmacokinetic parameters (geometric mean) in patients with advanced malignancies following a 14 mg/m² dose administered IV over a 4-hour period

C _{max} (ng/mL)	t _½ (hr)	AUC _∞ (ng*hr/mL)	Clearance (L/hr)	Volume of distribution (L)	T _{max} (hr) ^a
761	3.7	3157	8.4	44.5	3.0

^a median

Absorption: Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 to 24.9 mg/m² when administered intravenously over 4 hours in patients with advanced cancers.

Following a 4-hour infusion of 14 mg/m² dose, romidepsin plasma concentrations increased rapidly and reached a plateau (~90% of C_{max}) at approximately 1-hour post infusion initiation. At the end of infusion (ie, 4-hour), concentrations declined in an apparent multiphasic manner. Based on the non-compartmental analysis, romidepsin AUC_∞ [geometric mean (geometric CV%)] was 3,157 (33.9%) ng*hr/mL with a mean peak plasma concentration (C_{max}) of 761 (31.2%) ng/mL.

Distribution: Romidepsin is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1000 ng/mL with α 1-acid-glycoprotein (AAG) being the principal binding protein. Romidepsin is a substrate of the Pgp (ABCB1) and MRP1.

In vitro, romidepsin accumulates into human hepatocytes via an unknown active uptake process. Romidepsin is not a substrate of the following uptake transporters: BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. In addition, romidepsin is not an inhibitor of BCRP, MRP2, MDR1 or OAT3. Although romidepsin did not inhibit OAT1, OCT2, and OATP1B3 at concentrations seen clinically (1 μ mol/L), modest inhibition was observed at 10 μ mol/L. Romidepsin was found to be an inhibitor of BSEP and OATP1B1.

Metabolism: Romidepsin undergoes extensive metabolism *in vitro* primarily by CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19. At therapeutic concentrations, romidepsin did not competitively inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 *in vitro*. At therapeutic concentrations, romidepsin did not cause notable induction of CYP1A2, CYP2B6 and CYP3A4 *in vitro*. Therefore, pharmacokinetic drug-drug interactions are unlikely to occur due to CYP450 induction or inhibition by romidepsin when co-administered with CYP450 substrates.

Excretion: Following 4-hour intravenous administration of romidepsin at 14 mg/m², romidepsin clearance [geometric mean (geometric CV%)] was 8.4 (36.8) L/hr and terminal elimination half-life was 3.7 (8.3) hours. No accumulation of romidepsin was observed after repeated dosing.

Special Populations and Conditions

Pediatrics: No data are available.

Geriatrics, Gender and Race: The population pharmacokinetic analysis of romidepsin showed that age, gender and race did not appear to influence the pharmacokinetics of romidepsin.

Hepatic Insufficiency: No dedicated hepatic impairment study has been conducted for ISTODAX. The population pharmacokinetic analysis indicates that mild hepatic impairment [total bilirubin (TB) \leq upper limit of normal (ULN) and aspartate aminotransferase (AST) $>$ ULN; or TB $>$ 1.0x – 1.5x ULN and any AST] had no significant influence on romidepsin pharmacokinetics. The effect of moderate (TB $>$ 1.5x – 3x ULN and any AST) and severe (TB $>$ 3x ULN and any AST) hepatic impairment on the pharmacokinetics of romidepsin is unknown. Patients with moderate and severe hepatic impairment should be treated with caution.

Renal Insufficiency: No dedicated renal impairment study has been conducted for ISTODAX. The population pharmacokinetic analysis showed that romidepsin pharmacokinetics were not affected by mild (estimated creatinine clearance 50 – 80 mL/min), moderate (estimated creatinine clearance 30 – 50 mL/min), or severe (estimated creatinine clearance < 30 mL/min) renal impairment. The effect of end-stage renal disease on romidepsin pharmacokinetics has not been studied. Thus, patients with end-stage renal disease should be treated with caution.

STORAGE AND STABILITY

Storage:

Store at room temperature 15° to 30°C. Store vials of ISTODAX (romidepsin for injection) and supplied diluent together in carton until use.

Stability after reconstitution:

After reconstitution with supplied Diluent: at least 8 hours when stored at room temperature.

After dilution with 0.9% Sodium Chloride Injection, USP: up to 24 hours at room temperature. However, it should be administered as soon after dilution as possible.

SPECIAL HANDLING INSTRUCTIONS

ISTODAX (romidepsin for injection) should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ISTODAX (romidepsin for injection) is supplied as a kit containing two vials. ISTODAX is a sterile, lyophilized powder in a 10 mg single-use vial containing 11 mg of romidepsin and 22 mg of the bulking agent, povidone, USP. Diluent for ISTODAX is a sterile, clear solution and is supplied in a single-use vial containing 2.4 mL (2.2 mL deliverable volume) of 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP.

PART II: SCIENTIFIC INFORMATION

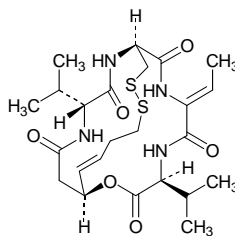
ISTODAX[®] (romidepsin), indicated for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	romidepsin
Chemical name:	(1 <i>S</i> ,4 <i>S</i> ,7 <i>Z</i> ,10 <i>S</i> ,16 <i>E</i> ,21 <i>R</i>)-7-ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone
Molecular formula and molecular mass:	C ₂₄ H ₃₆ N ₄ O ₆ S ₂ 540.71

Structural formula:



Physicochemical properties: Romidepsin, a histone deacetylase (HDAC) inhibitor, is a bicyclic depsipeptide. At room temperature, romidepsin is a white powder. It is very slightly soluble in water, sparingly soluble in dehydrated alcohol and acetone, and soluble in chloroform.

NOC/c CLINICAL TRIALS

Study demographics and trial design

ISTODAX (romidepsin for injection) was evaluated in a phase II, open-label, multicenter, single-arm, international clinical study in patients with PTCL [NOS (53%), AITL (21%) and ALK-1 negative ALCL (16%)]¹ who had failed at least 1 prior systemic therapy. Patients were treated with ISTODAX at a dose of 14 mg/m² infused over 4 hours on days 1, 8, and 15 every 28 days. Of the 131 patients treated, 130 patients had histological confirmation by independent central review and were evaluable for efficacy (HC Population). Six cycles of treatment were planned, responding patients had the option of continuing treatment beyond 6 cycles.

Primary assessment of efficacy was based on rate of complete response (CR=complete response + Cru= complete response unconfirmed) as determined by an Independent Review Committee (IRC) using the International Workshop Criteria (IWC).

Demographic and disease characteristics of the patients with PTCL are provided in [Table 5](#).

¹ Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALK-1, anaplastic lymphoma kinase-1;ALCL, anaplastic large-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma

Table 5: Baseline Patient Characteristics (PTCL Population)

Characteristic	Study GPI-06-0002 (N=130)
Age (years), n	
Mean (SD)	59 (13)
Median	61
Sex, n (%)	
Male	88 (68)
Female	42 (32)
Race, n (%)	
White	116 (89)
Black	7 (5)
Asian	3 (2)
Other	4 (3)
PTCL Subtype Based on Central Diagnosis, n (%)	
PTCL Unspecified (NOS)	69 (53)
Angioimmunoblastic T-cell lymphoma (AITL)	27 (21)
ALK-1 negative anaplastic large cell lymphoma (ALCL)	21 (16)
Other	13 (10)
Stage of Disease, n (%) ^a	
I/II	39 (30)
III/IV	91 (70)
ECOG Performance Status, n (%)	
0	46 (35)
1	67 (51)
2	17 (13)
Received Prior Systemic Therapy for PTCL	130 (100)
Number of Prior Systemic Therapies	
Median (Range)	2 (1, 8)
Received Prior Autologous Stem Cell Transplant	21 (16)
Received Prior Radiation Therapy	31 (24)

^a Stage of disease was reported at time of diagnosis

Study results

Efficacy outcomes for the HC population (n=130) as determined by the IRC and Investigators are provided in [Table 6](#) for Study GPI-06-0002. The complete response rate was 15% and overall response rate was 25% as determined by the IRC.

Table 6: Response Rates Based on Overall IRC Assessment (HC Population)

Response Rate	IRC (N=130)
ORR (CR+Cru+PR), n (%)	33 (25.4) [19.2] ^a
CR+Cru, n (%)	19 (14.6) [9.8] ^a
PR, n (%)	14 (10.8)
Stable Disease (SD)	33 (25.4)
Progressive Disease (PD)	35 (26.9)
Not Evaluable ^b	29 (22.3)
Duration of Response (months)	
ORR	
n	33
Median (range)	17 (<1 ^{c,d} , 34+ ^d)
CR + Cru	
n	19
Median (range)	17 (<13 ^d , 34+ ^d)

^a Lower bound of 95% Confidence Interval

^b Insufficient efficacy data to determine response due to early termination; included as non-responders in the analysis

^c One patient elected to go to transplant following the first response assessment of CR

^d Denotes censored value

DETAILED PHARMACOLOGY

Pharmacodynamics

In both *in vitro* and *in vivo* systems, romidepsin has been shown to elicit a range of biological activities, including HDAC inhibition, acetylation of histones and non-histone proteins, induction or repression of gene expression, cell cycle arrest, differentiation, cell growth inhibition, apoptotic cell death, morphological reversion of transformed cells, and inhibition of angiogenesis. Romidepsin most potently inhibits the Class I HDAC enzymes.

Pharmacokinetics

The pharmacokinetics of romidepsin have been conducted in rat and dog following intravenous administration, either as a bolus or an infusion. In vitro and in vivo studies using radiolabeled romidepsin were conducted to assess plasma protein binding, tissue distribution, metabolism and elimination. In both rats and dogs, the plasma disposition profile can best be described by a multiphasic curve on a log-linear plot of plasma concentration versus time. Romidepsin was rapidly eliminated from the plasma in rats and dogs. The initial distribution of romidepsin out of the plasma is rapid with distribution into many tissue and organ systems. The period following the initial distribution is characterized with $t_{1/2}$ estimates ranging from less than 1 hour in rats to more than 4 hours in dogs. Exposure to romidepsin appears to be linear over the dose ranges tested and there are no consistent gender differences in the exposure or plasma kinetics.

Following a single radiolabeled romidepsin intravenous dose to rats, radioactivity rapidly distributed to virtually all tissues, with very low concentrations of radioactivity reaching the brain. Romidepsin is highly protein bound in both human serum (94% to 95%) and human plasma (92% to 94%) over the concentration range of 50 to 1000 ng/mL. The percentages of romidepsin bound to human serum albumin and AGP were 19.9% and 93.5%, respectively, suggesting that the principal binding protein in human serum is AGP.

In vitro in liver microsomes and S9 fractions, romidepsin was extensively metabolized with approximately 30 different metabolites identified in rats, dogs, and humans. The metabolite profile was similar in the rat, dog, and human. No single metabolite accounted for greater than 5% of the total. In vitro cytochrome P450 (CYP) isoforms involved in romidepsin metabolism were assessed using human liver microsomes and cDNA-expressed human CYPs and the results indicate that romidepsin is a substrate for CYP3A4 with only minor activity from CYP3A5, 1A1, 2B6, and 2C19. Other P450 subtypes showed no significant metabolic activity toward romidepsin.

The primary route of elimination of romidepsin derived radioactivity was through bile with subsequent excretion into feces in rat. Approximately 96% of the dose recovered in the excreta, with less than 20% of the total drug derived radioactivity was eliminated in urine while less than 5% of the radioactivity dose is accounted for by the parent drug.

TOXICOLOGY

Acute Toxicity

Based on the single dose studies in rats and dogs, acute toxic effects of romidepsin consisted of respiratory, cardiac, and central nervous system (CNS)/neurotoxicities.

Single-dose intravenous LD₅₀ in rats was estimated to be greater than 2.6 mg/kg (15.6 mg/m²) for both males and females. Single intravenous doses of 0.1 to 1.0 mg/kg (2 to 20 mg/m²) in the dog resulted in no deaths. Clinical signs of toxicity in dogs included decreased spontaneous motility, congestion of eye mucosa, vomituous, irregular respiration, irregular heart rate, cough, and salivation. In addition, leukopenia, lymphocytopenia, hyperglycemia, hyperlipidemia, hypocalcemia and hypokalemia were observed in dogs following the IV administration of romidepsin. Atrophy of the thymus accompanied by decreased cortical lymphocytes and thymus weight were observed. A single administration of romidepsin at the dose level of 20 mg/m² to beagle dogs had effects on cardiovascular and respiratory systems at a dose level comparable to the proposed human dose.

Repeat Dose Toxicity

Romidepsin was administered under various dosing schedules to rats and dogs. Deaths occurred at doses of 1.0 mg/kg (6.0 mg/m²) in rats and 2.0 mg/kg (40 mg/m²) in dogs.

The toxicity profile for romidepsin in rats was consistent whether administered once weekly for 3 weeks or as a cycle of 3 weekly administrations with 1 week off for 26 weeks. Principle target organs in rats were the injection site, lymphoid organs, the hematopoietic system and reproductive organs. Typical findings in rats at the injection site following infusion of romidepsin included thickening and swelling at the injection site with microscopic findings consisting of inflammation, edema, hemorrhage, and/or necrosis. Lymphocyte depletion was noted in the thymus, spleen, and lymph nodes along with bone marrow hypocellularity. This correlated with reductions in white blood cells driven by a decrease in circulating lymphocytes. A regenerative anemia was common in rats administered romidepsin. Platelets were decreased in rats, with an increase in mean platelet volume. The administration of romidepsin by 3-times monthly intravenous bolus injection for 26 weeks at dose levels of 0, 0.1, 0.33, and 0.67/1.0 mg/kg (0.60 to 6.0 mg/m²) resulted in treatment-related effects at all dose levels. Repeated doses of intravenous romidepsin lowered WBCs, WBC differentials, lymphocytes, and basophil counts. Romidepsin-related changes in organ weight were reported in the thymus, pituitary, ovary and uterus; macroscopic changes were noted in thymus, ovary, and pituitary. Pathological changes were noted in bone marrow, spleen, thymus, liver, pituitary, ovary, uterus, vagina, mammary gland, and testis, suggesting that target organs in the rat include the hematopoietic system, thymus, pituitary, and reproductive organs. Based on the presence of test article-related histopathological findings at all dose levels, a NOAEL was not determined. Most changes were at least partially reversible following a recovery period of two weeks.

When administered weekly as an intravenous 4-hour infusion, romidepsin was tolerated in dogs at doses up to 20 mg/m². This dose was tolerated when administered up to twice weekly for a total weekly dose of 40 mg/m²; however a single dose of 40 mg/m² was not well tolerated. Toxicity was noted at total weekly doses as low as 2.0 mg/m². An NOAEL for romidepsin was not determined in dogs.

Principle target organs in the dog were the injection site, gastrointestinal (GI) tract, lymphoid organs, hematopoietic system, reproductive organs, and cardiovascular system.

Romidepsin exacerbated pathology findings at the injection/catheter site of dogs in a dose-dependent manner. Typical findings included thickening and swelling at the injection site with microscopic findings consisting of inflammation, edema, hemorrhage, and/or necrosis. Romidepsin caused an increase in emesis and diarrhea, particularly at $\geq 10 \text{ mg/m}^2$. Mucosal epithelial degeneration was noted in multiple tissues of the GI tract at $\geq 10 \text{ mg/m}^2$. Lymphoid depletion was apparent in the thymus, lymph nodes, tonsil, and spleen along with bone marrow hypocellularity. This correlated with reductions in circulating white blood cells driven by a decrease in lymphocytes. A mild anemia was common in dogs administered romidepsin. There was no effect on platelet counts in the dog. Cardiotoxicity signs in dogs administered romidepsin included irregular rhythm, heart rate-corrected QT interval (QTc) prolongation. Foci with hemorrhage were observed occasionally at 1.0 mg/kg (20 mg/m^2), but mostly at the non-tolerated dose of 2.0 mg/kg (40 mg/m^2), where drug was administered every 4 days. Effects of romidepsin on reproductive organs are discussed in the sections on impairment of fertility. Most changes were at least partially reversible following a recovery period of two weeks.

Changes in serum chemistry results also demonstrated some consistency across studies and species. In both rats and dogs, ALT, AST, ALP, and fibrinogen were often increased following romidepsin dosing. Dogs also demonstrated increased cholesterol, CK, and LDH, and decreased BUN and electrolytes, whereas the rat studies were inconsistent with regard to BUN. Most serum chemistry effects were reversible in both species.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with romidepsin. Romidepsin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test). In the mouse lymphoma cell mutation assay, romidepsin at concentrations up to $0.3 \text{ }\mu\text{g/mL}$ exhibited very weak mutagenic activity in mouse lymphoma L5178Y cell. The low magnitude of the activity, while statistically significant, is unlikely to be of biological significance for this class of compound. Romidepsin was not clastogenic in an *in vivo* rat bone marrow micronucleus assay when tested to the maximum tolerated dose (MTD) of 1 mg/kg in males and 3 mg/kg in females (6 and 18 mg/m^2 in males and females, respectively). These doses were up to 1.3-fold the recommended human dose, based on body surface area

Impairment of Fertility

Data from repeat-dose toxicity studies indicated that romidepsin may cause irreversible infertility in humans (see **WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**).

The administration of romidepsin to rats, mice and dogs produced macroscopic and microscopic changes in reproductive organs. In male mice, dose dependent testicular atrophy was noted and found to persist for at least 3 weeks after the termination of treatment. In male rats, seminal vesicle and prostate organ weights were decreased at 4 weeks after treatment cessation suggesting the lack of reversibility. In dogs, romidepsin

administration at doses $\geq 20 \text{ mg/m}^2$ was associated with hypospermia in the testes and epididymides, and seminiferous tubule degeneration; recovery was not demonstrated. In female rats, maturation arrest of ovarian follicles and decreased weight of ovaries were observed in all animals that had received 0.6 mg/m^2 /day for 4 consecutive weeks. This dose is approximately 30% the estimated human dose. The changes in the ovaries did not recover over a 4-week recovery period. In a 26-week toxicology study in rats, romidepsin administration resulted in testicular degeneration at 2 mg/m^2 dose following the clinical dosing schedule. This dose resulted in exposure of approximately 1% the exposure level in patients receiving the recommended dose of 14 mg/m^2 . In female rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females at 0.6 mg/m^2 following the clinical dosing schedule which resulted in exposure of 0.3% the human exposure.

Romidepsin showed affinity for binding to estrogen receptors in pharmacology studies. Romidepsin may interfere with hormonal contraceptives, resulting in high-risk pregnancies.

Developmental Toxicology

In embryo-fetal developmental toxicity studies romidepsin treatment was associated with developmental toxicity, teratogenicity, and pregnancy loss at subtherapeutic doses that resulted in a total weekly exposure approximately 2% of the recommended clinical dose.

In pregnant Sprague Dawley rats administered romidepsin during organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day ($0.6, 1.2$ and 3.0 mg/m^2 , respectively) maternal and developmental toxicity was observed. The systemic exposures in pregnant rats were 1-8% of the human exposure at the recommended clinical dose of 14 mg/m^2 once weekly. Maternal findings included adverse clinical signs, a dose-dependent reduction in body weight gain and feed consumption at $\geq 0.1 \text{ mg/kg/day}$ ($\geq 0.6 \text{ mg/m}^2$ or AUCt 2.44 ng.hr/mL). There were reduced gravid uterine weight and corrected maternal body weight at $\geq 0.6 \text{ mg/m}^2$. Adverse embryo-fetal effects included early resorptions, reduced fetal body weights, increased fetal and litter incidences of rotated hindlimbs and folded retina, delayed ossifications and significant ($p \leq 0.01$) increases in the incidence of supernumerary thoracic ribs at doses $\geq 0.1 \text{ mg/kg/day}$ ($\geq 1.2 \text{ mg/m}^2$ or AUCt 4.99 ng.hr/mL). Two fetuses from different litters in the 0.2 mg/kg/day dosage group had an absent innominate artery at visceral examination. One of these fetuses also had an interrupted aortic arch. Based on the results of all developmental toxicity studies, the maternal and the fetal NOAEL was as low as 0.006 mg/kg (0.036 mg/m^2).

SAFETY PHARMACOLOGY

In single dose safety pharmacology studies, the highest intravenous dose levels tested *in vivo* was 6 mg/m^2 and 20 mg/m^2 in rats and dogs, respectively. In these studies, dose-related physiological effects were observed on both the central nervous and cardiovascular systems following romidepsin administration, although they were generally observed for no longer than 24 hours after dose administration. Central nervous system effects were generally mild and included increases in body temperature of up to $1.6 \text{ }^\circ\text{C}$ and spontaneous locomotor activity. In dogs, a dose of 20 mg/m^2 caused a

significant increase in heart rate of 34% that persisted for 4.5 to 10 hours post-infusion. No effects on PR interval and QRS duration were noted. Other relevant findings at 20 mg/m² included slight prolongation of QTc of 8% to 5%, which was observed at 24 hours after dosing. There were no cardiovascular findings at doses of 6 mg/m². In a repeat dose toxicity study in dogs that evaluated electrocardiography (ECG) parameters, romidepsin was administered as a 4-hour infusion once weekly for 3 weeks at 6 and 20 mg/m², followed by a 2-week recovery period. An increase in heart rate and QT prolongation was observed in both dose groups. QT prolongation occurred 24 hours after dosing but resolved following the 2-week recovery period. These changes in the heart rate and the QT interval were not associated with any abnormal cardiac-specific histopathology findings.

Therapeutically relevant concentrations of romidepsin had no effect on the action potential in the guinea pig model. Romidepsin suppressed the hERG channel current by 18% at 1 µg/mL and 37% at 10 µg/mL. However, the degree of channel current suppression (8%) caused by romidepsin at therapeutically relevant concentrations of 0.3 µg/mL was not significant, therefore the potential of romidepsin to suppress the hERG current is low.

REFERENCES

1. Acharya MR, Sparreboom A, Venitz J, Figg W. Rational Development of Histone Deacetylase Inhibitors as Anticancer Agents: A Review. *Molecular Pharmacology* 2005;68(4):917-932.
2. Ascani S, Zinzani PL, Gherlinzoni F, et al. Peripheral T-cell lymphomas: clinico-pathologic study of 168 cases diagnosed according to the R.E.A.L. classification. *Ann Oncol*. 1997;8:583-92.
3. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 2012;30(6):631-636.
4. Dearden CE, Foss FM. Peripheral T-cell lymphomas: diagnosis and management. *Hemat Oncol Clin North Am* 2003;17(6):1351-1366.
5. Grant C, Rahman F, Piekarz R, Peer C, Frye R, Robey RW, et al. Romidepsin: a new therapy for cutaneous T-cell lymphoma and a potential therapy for solid tumors. *Expert Rev Anticancer Ther* 2010;10(7):997-1008.
6. Greer JP, York JC, Cousar, JB, Mitchell, RT, Flexner JM, Collins RD, et al. Peripheral T-cell lymphoma: a clinicopathologic study of 42 cases. *J Clin Oncol* 1984;2(7):788-798.
7. Piekarz RL, Frye R, Prince HM, Kirshbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 2011; 117(22):5827-5834.
8. Piekarz RL, Frye R, Turner M, Wright J, Allen S, Kirschbaum MH, et al. Update of the NCI multi-institutional phase II trial of romidepsin, FK228, for patients with cutaneous or peripheral T-cell lymphoma. *J Clin Oncol* 2007;25(18S):8027.
9. Rodriguez-Abreu D, Filho VB, Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. *Hematol Oncol* 2008; 26: 8–20.
10. Rodriguez J, Guitierrez A, Martinez-Delgado B, Peres-Manga G. Current and future aggressive peripheral T-cell lymphoma treatment paradigms, biological features and therapeutic molecular targets. *Crit Rev Oncol Hematol* 2009;71(3):181-198.
11. Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2010;28(29):4485-4491.

PART III: CONSUMER INFORMATION

ISTODAX® (romidepsin is indicated for the treatment of patients with peripheral T-cell lymphoma (PTCL) who cannot receive a stem cell transplant and have disease which has come back after other attempted treatment by your physicians, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada’s NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

PrISTODAX
romidepsin for injection

This leaflet is part III of a three-part "Product Monograph" published when ISTODAX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ISTODAX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ISTODAX is a prescription medicine used to treat people with a type of blood cancer called peripheral T-cell lymphoma (PTCL) who cannot receive a stem cell transplant, after at least one other type of medicine by mouth or injection has been tried.

What is peripheral T-cell lymphoma:

Peripheral T-cell lymphoma (PTCL) is a disease in which certain cells of the lymph system called T-cells develop into cancer cells which develop and grow abnormally. The term “peripheral” means that this cancer develops in mature T-cells outside of the bone marrow such as lymph nodes, spleen, gastrointestinal tract, and skin. It is often not known why someone develops PTCL.

What it does:

ISTODAX belongs to a group of medicines called cytostatic drugs which work by preventing the growth of cancer cells.

When it should not be used:

Do not use ISTODAX if you are allergic to romidepsin or to any of the other ingredients of ISTODAX.

What the medicinal ingredient is:

romidepsin

What the important nonmedicinal ingredients are:

Povidone. The diluent contains 80% propylene glycol and 20% dehydrated alcohol.

What dosage forms it comes in:

ISTODAX is supplied as a sterile freeze-dried powder. Each vial delivers 10 mg of romidepsin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ISTODAX should only be prescribed by a doctor experienced in the use of anti-cancer drugs. Serious side effects may occur with the use of ISTODAX and could include:

- decrease in the production of blood cells resulting in very low levels of red blood cells, white blood cells, and platelets (pancytopenia)
- abnormal heart beat (QTc prolongation)
- life-threatening infections (including pneumonia and sepsis)
- tumor lysis syndrome due to rapid breakdown of cancer cells; this can result in damage to the kidneys, heart and liver
- birth defects or death of an unborn baby

ISTODAX has not been studied in patients with liver or kidney disease.

BEFORE you use ISTODAX talk to your doctor or pharmacist if you:

- have kidney problems
- have liver problems
- have nausea, vomiting, or diarrhea
- have any other medical conditions
- have any heart problems, including an irregular or fast heartbeat
- have QT/QTc prolongation or a family history of QT/QTc prolongation;
- have heart disease
- have a personal history of fainting spells
- have a family history of sudden cardiac death at <50 years
- have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- have had previous viral infection (e.g. hepatitis B, cytomegalovirus (CMV), herpes, Epstein-Barr virus)
- are pregnant or plan to become pregnant. ISTODAX may harm your unborn baby. Talk to your doctor about the best way to prevent pregnancy while taking ISTODAX. Tell your doctor right away if you become pregnant while taking ISTODAX.
- are breastfeeding or plan to breastfeed. It is not known if ISTODAX passes into your breast milk. You should not breast feed your baby if you are being treated with ISTODAX.

It is not known if ISTODAX is safe and effective in children under 18 years of age.

ISTODAX has an effect on the electrical activity of the heart known as QT/QTc prolongation. This effect can be measured as a change in the electrocardiogram (ECG). In very rare cases, drugs with this effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. In general, females and people more than 65 years in age are at higher risk. It is important to

follow the instructions of your doctor with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

Electrocardiograms (ECGs) and blood tests may be required periodically to monitor the risk of potentially serious side effects during treatment with ISTODAX.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Some medicines may affect how ISTODAX works, or ISTODAX may affect how your other medicines work.

Drugs that may interact with ISTODAX include:

- Blood thinner medicine (e.g. warfarin sodium). Ask your doctor if you are not sure if you are taking a blood thinner. Your doctor may want to test your blood more often.
- Drugs to treat abnormal heart beats (e.g. quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide, propafenone).
- Drugs to treat schizophrenia and other psychiatric disease (e.g. chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- Birth control that contains estrogen; such as the “pills”, patches, implants, or Intrauterine devices (IUDs). ISTODAX may reduce the effectiveness of estrogen-containing contraceptives. You may become pregnant.
- St. John’s Wort (*Hypericum perforatum*), an herbal treatment for depression
- Domperidone, used to treat gastrointestinal disorder.
- Methadone (an opioid)
- Medicine for:
 - depression (e.g. fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine, maprotiline)
 - bacterial infections (antibiotics such as erythromycin, clarithromycin, telithromycin, tacrolimus, moxifloxacin, levofloxacin, ciprofloxacin)
 - malaria (e.g. quinine, chloroquine)
 - fungal infections (e.g. ketoconazole, fluconazole, voriconazole)
 - nausea (e.g. dolasetron, ondansetron)

- cancer (e.g. vandetanib, sunitinib, nilotinib, lapatinib, vorinostat)
- asthma (e.g. salmeterol, formoterol)

Any medicine that cause imbalance in the electrolytes in your body:

- diuretics (water pills)
- laxatives and enemas
- amphotericin B
- high dose corticosteroids

This list includes some, but not all, of the drugs that may increase the risk of side effects while receiving ISTODAX.

Tell your doctor or pharmacist if you are taking these or any other medicines even those not prescribed (including any over the counter drugs, vitamins, or herbal medicines).

PROPER USE OF THIS MEDICATION

Usual dose:

ISTODAX will be given to you by a healthcare provider as an intravenous (IV) injection into your vein usually over 4 hours.

ISTODAX is usually given on Day 1, Day 8, and Day 15 of a 28 day cycle of treatment.

Your doctor will decide how long you will receive treatment with ISTODAX.

Your doctor will check your blood cell counts and will perform other blood tests regularly during your treatment with ISTODAX. Your doctor may decide to do further tests to check your health as needed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

This medicine needs to be given on fixed schedule. If you miss an appointment, call your doctor for instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ISTODAX may cause serious side effects, including:

- **Low blood cell counts:** Your doctor will regularly do blood tests to check your blood counts.
 - **Low platelets:** can cause unusual bleeding, or bruising under the skin. Talk to your doctor right away if this happens.

- **Low red blood cells:** may make you feel tired and you may get tired easily. You may look pale, and feel short of breath. Tell your doctor if you have these symptoms.

- **Low white blood cells:** can cause you to get infections, which may be serious. Your chance of life-threatening infections may be higher if you have received chemotherapy. Infection can also happen with normal white blood cell counts.

- Tell your doctor right away if you have any of these symptoms: fever, cough, flu-like symptoms, burning on urination, muscle aches, or worsening of skin problems.

- **Changes in the electrical activity of your heart seen on ECG (electrocardiogram).** Your doctor may check your ECG as needed for this problem. Tell your doctor if your feel an abnormal heart beat, chest pain or shortness of breath.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting, or seizures, you should seek immediate medical attention.

- **Tumor Lysis Syndrome (TLS).** TLS can occur during treatment as a complication of the rapid breakdown of cancer cells. Your doctor may do blood tests to check for TLS and may give you medicine to prevent or treat TLS.

Common side effects of ISTODAX include:

- nausea, vomiting, diarrhea, constipation, and loss of appetite
- tiredness

Tell your doctor if you have any side effect that bothers you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Fever/Neutropenia (low white blood cells)		✓	
Common	Tiredness/Anemia (low red blood cells)		✓	

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Bleeding from the gums or other sites or abnormal bleeding/Thrombocytopenia (low platelets that help with blood clotting)		✓	
Common	Signs of infection: fever, significant fatigue, shortness of breath, cough, burning on urination, flu-like symptoms, muscle aches, worsening skin problems		✓	
Uncommon	Vomiting		✓	
Rare	Irregular or abnormal heart beats			✓
Rare	Symptoms of tumor lysis syndrome: lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures			✓

This is not a complete list of side effects. For any unexpected effects while taking ISTODAX, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 to 30°C). Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The information in this document is current as of the last revision date shown below. The most current information can be found at: <http://www.celgenecanada.net> or by contacting the sponsor, Celgene Inc. at: 1-888-712-2353.

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