PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrISTODAX®

romidepsin for injection

Lyophilized powder for solution, 10 mg/vial, intravenous infusion

Antineoplastic Agent
Histone Deacetylase (HDAC) Inhibitor

ISTODAX® (romidepsin) 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

has been issued market authorization with conditions. The clinical benefit of ISTODAX in the relapsed/refractory PTCL setting remains unconfirmed. Patients and Health Care Professionals should be advised of the Restricted Access Program. ISTODAX should not be initiated in new patients outside of an investigational setting. For further information for ISTODAX please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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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 authorized 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.

RECENT MAJOR LABEL CHANGES

1 Indications	03/2023
3 Serious Warnings and Precautions Box	03/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 14 CLINICAL TRIALS). Improvement in overall survival has not been demonstrated with ISTODAX. The clinical benefit of ISTODAX in the relapsed/refractory PTCL setting remains unconfirmed. ISTODAX should not be initiated in new patients outside of an investigational setting.

Distribution Restriction

ISTODAX is only available through the Restricted Access Program to patients currently receiving treatment with ISTODAX. Prescribers must register their patients under the Restricted Access Program to prescribe and dispense the product. ISTODAX will be withdrawn from the Canadian Market after the last patient terminates treatment with ISTODAX. For more information on the Restricted Access Program, contact Medical Information Services at 1-866-463-6267 and medical.canada@bms.com.

1.1 Pediatrics

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

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

- ISTODAX is contraindicated in patients who are hypersensitive to romidepsin or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 7 WARNINGS AND PRECAUTIONS) • QT interval prolongation (see 7 WARNINGS AND PRECAUTIONS) • Fatal infections (see 7 WARNINGS AND PRECAUTIONS)

- Tumor lysis syndrome (see 7 WARNINGS AND PRECAUTIONS)
- Potential fetal harm (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY)
- Hepatic impairment (see 7 WARNINGS AND PRECAUTIONS Special Populations)

ISTODAX has not been studied in patients with renal impairment.

- Available only under the Restricted Access Program (see 1 INDICATIONS, Distribution Restriction)

4 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.

4.1 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 end stage renal function.
- Dosage given should be adjusted according to tolerability as described below.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose is 14 mg/m^2 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/m^2. 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/m^2.
- 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/m^2.
- 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 ≥ 1.5×10^9/L and/or platelet count ≥75×10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with ISTODAX should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m^2.

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

- The use of ISTODAX is not recommended in patients with severe hepatic impairment (bilirubin level > 3 x upper limit normal (ULN) and any AST) (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment).
- In patients with moderate hepatic impairment (bilirubin level > 1.5 x ULN to ≤ 3 x ULN, and any AST), reduce the starting dose of ISTODAX to 7 mg/m^2 (50% reduction) (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment).
- Dose adjustment of ISTODAX is not required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > ULN but ≤ 1.5 x ULN, and any AST) (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).
- The risk of adverse effects associated with ISTODAX may be increased in patients with hepatic impairment. Monitor patients for signs of toxicity (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

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 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

4.3 Reconstitution

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 vial for injection. 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.

4.4 Administration

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.

4.5 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.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage 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 16 NON-CLINICAL 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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder for solution, 10 mg romidepsin per vial	dehydrated alcohol, povidone, propylene glycol

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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 8 ADVERSE REACTIONS and 9 DRUG INTERACTIONS Drug-Behavioural Lifestyle Interactions).

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with romidepsin (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

QTc Prolongation and Electrocardiographic Changes: ISTODAX has been associated with QTc interval prolongation (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 10 CLINICAL PHARMACOLOGY, Pharmacodynamics). 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 9 DRUG INTERACTIONS).

Heart Rate: ISTODAX is associated with an increase in heart rate (see 10 CLINICAL PHARMACOLOGY, Pharmacodynamics). 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 9 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 9 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 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

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.

Immune

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).

Metabolism and Nutrition Disorders

Tumour 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.

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 4 DOSAGE AND ADMINISTRATION and 8 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9 DRUG INTERACTIONS; 10 CLINICAL PHARMACOLOGY, Pharmacodynamics).

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 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, 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.

Reproductive Health: Female and Male Potential

- **Fertility**

  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 16 NON-CLINICAL TOXICOLOGY). These changes may be irreversible. Patients should be advised that their sexual function/reproduction may be compromised by the treatment with ISTODAX.

- **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). Females of childbearing potential should have a pregnancy test prior to starting treatment with ISTODAX.

  Due to the potential hazard to the fetus, females of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ISTODAX.-Effective 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 9 DRUG INTERACTIONS, Drug-Drug Interactions).

  Non-clinical findings suggest that ISTODAX can bind to the estrogen receptor and thus may modulate estrogen signaling (see 16 NON-CLINICAL TOXICOLOGY. It is not known if romidepsin has any estrogenic or anti-estrogenic effects.

- **Male Patients**

  It is not known if romidepsin is present in semen. Male patients are advised to use effective contraception and to avoid fathering a child during and up to 1 month after 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 16 NON-CLINICAL TOXICOLOGY). Semen preservation prior to initiation of ISTODAX therapy could be considered.

Sensitivity/Resistance

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

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 9 DRUG INTERACTIONS, Drug-Drug Interactions).

7.1 Special Populations

7.1.1 Pregnant Women

ISTODAX should not be used during pregnancy. Based on its mechanism of action and findings in animals, ISTODAX can 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 16 NON-CLINICAL TOXICOLOGY).

ISTODAX may reduce the effectiveness of estrogen-containing contraceptives (see 9 DRUG INTERACTIONS).

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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.

7.1.5 Hepatic Impairment

ISTODAX is not recommended in patients with severe hepatic impairment as the safe dose of romidepsin has not been established for this patient population (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions). Based on the results of a hepatic impairment study, no dose adjustment is recommended for patients with mild hepatic impairment. If the benefit is considered to outweigh the risk in a patient with moderate hepatic impairment, a 50% reduction of the starting dose to 7 mg/m^2 is recommended (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions). The risk of adverse effects associated with ISTODAX may be increased in patients with hepatic impairment. Monitor patients for signs of toxicity (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

8 ADVERSE REACTIONS

8.1 Adverse 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/m^2. 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 7 WARNINGS AND PRECAUTIONS, Immune).

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2 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 2: Adverse Drug Reactions Occurring in ≥5% of Patients with PTCL in Study GPI-06-0002 (N=131)

	Study GPI-06-0002	
Adverse Reactions	**All**	**Grade 3 or 4**
Any adverse reactions	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)

Adverse Reactions	Study GPI-06-0002	
	All	Grade 3 or 4
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

Adverse Reactions	Study GPI-06-0002	
	All	Grade 3 or 4
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)
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

Adverse Reactions	Study GPI-06-0002	
	All	Grade 3 or 4
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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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 3 for both hematology and chemistry parameters.

Table 3: 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)

Laboratory Parameter	Study GPI-06-0002	
	All Shifts [1] n/N (%)	Grade 3 or 4 [2] n/N (%)
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)

8.5 Post-Market Adverse 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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

9.3 Drug-Behavioural 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 8 ADVERSE REACTIONS). If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	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 *in vitro* 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 7 WARNINGS AND PRECAUTIONS, Pregnant Women). 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

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 Cmax, 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.

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 7 WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; 10 CLINICAL PHARMACOLOGY, Pharmacodynamics).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

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

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

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/m^2 as a 4-hour intravenous infusion, and at doses of 8, 10 or 12 mg/m^2 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; 9 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/m^2 as a 4-hour infusion. At 24 hours after the start of romidepsin infusion, the mean increase in heart rate was 1.4 bpm.

Detailed 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.

10.3 Pharmacokinetics

Table 5: Summary of romidepsin pharmacokinetic parameters (geometric mean) in patients with advanced malignancies following a 14 mg/m^2 dose administered IV over a 4-hour period

	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{½}$ (h)	AUC_{∞} (ng*hr/mL)	CL (L/hr)	Vd (L)
14 mg/m^2	761	3.0	3.7	3157	8.4	44.5

[a] median

Absorption:

Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 to 24.9 mg/m^2 when administered intravenously over 4 hours in patients with advanced cancers.

Following a 4-hour infusion of 14 mg/m^2 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 α1-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 µmol/L), modest inhibition was observed at 10 µmol/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.

Elimination:

Following 4-hour intravenous administration of romidepsin at 14 mg/m^2, 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, Sex and Ethnic origin: The population pharmacokinetic analysis of romidepsin showed that

age, sex and ethnic origin did not appear to influence the pharmacokinetics of romidepsin.

Hepatic Insufficiency: Following a single 4-hour intravenous infusion dose administration of romidepsin 14 mg/m^2, 7 mg/m^2, and 5 mg/m^2 in patients with mild, moderate, and severe hepatic impairment, the geometric mean C_{max} values were approximately 115%, 96%, and 95% of the corresponding value after administration of 14 mg/m^2 romidepsin in patients with normal hepatic function, respectively. The geometric mean AUC_{inf} values in patients with mild, moderate, and severe hepatic impairment were approximately 144%, 114%, and 116%, respectively of the corresponding value in patients with normal hepatic function. Consistent with the overall exposure (AUC_{inf}) results, compared to the normal hepatic function cohort, romidepsin clearance decreased with an increased severity of hepatic impairment. Hence, dosage adjustment is recommended for patients with moderate hepatic dysfunction. Romidepsin is not recommended for patients with severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION).

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.

Detailed 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.

11 STORAGE, STABILITY AND DISPOSAL

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.

12 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

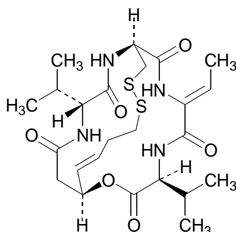
Drug Substance

Proper name: romidepsin

Chemical name: (1*S*,4*S*,7*Z*,10*S*,16*E*,21*R*)-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: $C_{24}H_{36}N_4O_6S_2$ 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 - Summary of patient demographics for clinical trials in relapsed/refractory PTCL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
GPI-06-0002	Phase II, open-label, multicenter, single-arm, international clinical study	Dose of 14 mg/m^2 infused over 4 hours on days 1, 8, and 15 every 28 days.	131	59 (20, 83)	Male: 88 Female: 42

Summary of GPI-06-0002

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/m^2 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 7.

Table 7: 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)

[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

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.

14.2 Study Results

Efficacy outcomes for the HC population (n=130) as determined by the IRC and Investigators are provided in Table 8 for Study GPI-06-0002. The complete response rate was 15% and overall response rate was 25% as determined by the IRC.

Table 8: 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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 LD_{50} in rats was estimated to be greater than 2.6 mg/kg (15.6 mg/m^2) for both males and females. Single intravenous doses of 0.1 to 1.0 mg/kg (2 to 20 mg/m^2) in the dog resulted in no deaths. Clinical signs of toxicity in dogs included decreased spontaneous motility, congestion of eye mucosa, vomitous, 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/m^2 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/m^2) in rats and 2.0 mg/kg (40 mg/m^2) 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/m^2) 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/m^2. This dose was tolerated when administered up to twice weekly for a total weekly dose of 40 mg/m^2; however, a single dose of 40 mg/m^2 was not well tolerated. Toxicity was noted at total weekly doses as low as 2.0 mg/m^2. 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 ≥ 10 mg/m^2. Mucosal epithelial degeneration was noted in multiple tissues of the GI tract at ≥10 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.

Carcinogenicity and Genotoxicity:

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 µg/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.

Reproductive and Developmental Toxicology:

Impairment of Fertility

Data from repeat-dose toxicity studies indicated that romidepsin may cause irreversible infertility in humans (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health).

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 ≥ 20 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 ≥0.1 mg/kg/day (≥0.6 mg/m^2 or AUCt 2.44 ng.hr/mL). There were reduced gravid uterine weight and corrected maternal body weight at ≥ 0.6 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 ≥ 0.1 mg/kg/day (≥1.2 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 ºC 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/m^2 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/m^2. 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/m^2, 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ISTODAX®

romidepsin for injection

Read this carefully before you start taking **ISTODAX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ISTODAX**.

Serious Warnings and Precautions

ISTODAX should only be prescribed by a healthcare professional experienced in the use of anti-cancer drugs. ISTODAX is only offered through the Restricted Access Program. A healthcare professional must register current patients under the program to receive ISTODAX. ISTODAX will be removed from the Canadian Market after the last patient ends treatment with ISTODAX. For more information on the Restricted Access Program, contact Medical Information Services at 1-866-463-6267 and medical.canada@bms.com.

Serious side effects may occur with the use of ISTODAX and could include:

- **QTc prolongation** (abnormal heart beat like rapid or pounding heart beat). This can also cause dizziness, fainting, seizures or death. Contact your healthcare professional right away if you experience these symptoms.
- **Pancytopenia** (decrease in red and white blood cells and platelets). Your healthcare professional will monitor your blood health before and during treatment;
- **Infections** that are life-threatening (including **pneumonia** and **sepsis**). ISTODAX can reactivate other viruses like Epstein Barr, hepatitis B, and cytomegalovirus (CMV);
- **Tumor lysis syndrome** (rapid breakdown of cancer cells); this can result in damage to the kidneys, heart and liver. Your healthcare professional will monitor and treat you as needed;
- **Birth defects** or **death** of an unborn baby;
- **Liver problems.** ISTODAX is not recommended if you have severe liver disease.

ISTODAX has not been studied in patients with kidney disease.

What is ISTODAX used for?

For the following indication ISTODAX has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

ISTODAX is used to treat adults with a type of blood cancer called peripheral T-cell lymphoma (PTCL) who:

- cannot receive a stem cell transplant, and
- have tried at least one other type of treatment by mouth or injection.

No additional studies are available to confirm if ISTODAX helps with survival or slowing down the disease. For more information, talk to your healthcare professional.

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

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does ISTODAX work?
ISTODAX belongs to a group of medicines called cytostatic drugs. These work by preventing the growth of cancer cells.

What are the ingredients in ISTODAX?

Medicinal ingredients: romidepsin
Non-medicinal ingredients: dehydrated alcohol, povidone, propylene glycol

ISTODAX comes in the following dosage forms:
Sterile freeze-dried powder: 10 mg

Do not use ISTODAX if:

- You are allergic to romidepsin or to any of the other ingredients of ISTODAX

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ISTODAX. Talk about any health conditions or problems you may have, including if you:

- have kidney problems
- have liver problems

- have nausea, vomiting, or diarrhea
- have any other medical conditions
- have the following risks for abnormal heart beat:
    - you are female
    - you are 65 years old or older
    - have any heart problems, or a family history of heart problems
    - have a family history of sudden cardiac death at < 50 years
    - have or have a family history of irregular or fast heartbeat, including QT/QTc prolongation
    - have a personal history of fainting spells
    - have electrolyte problems (like low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (like vomiting, diarrhea, dehydration)
    - have diabetes
    - have nervous system or brain problems
- have had previous viral infection (e.g. hepatitis B, cytomegalovirus (CMV), herpes, Epstein-Barr virus)
- have bone marrow problems
- have a history of chemotherapy

Other warnings you should know about:

Pregnancy and breastfeeding:
Female Patients:

- If you are pregnant or plan to become pregnant, there are specific risks you should discuss with your doctor.
- Avoid becoming pregnant while receiving ISTODAX. It may harm your unborn baby or may cause you to lose the pregnancy.
- You should use effective non-hormone methods of birth control while receiving ISTODAX. Keep using birth control for 8 weeks after your last dose of ISTODAX. Tell your healthcare professional right away if you become pregnant while taking ISTODAX.
- **For women who can get pregnant:** a pregnancy test should be done before you start treatment with ISTODAX.
- 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.

Male Patients:

- You should father a child while you are receiving ISTODAX.
- You should use effective contraception to prevent pregnancy in your partner while you are receiving ISTODAX.
    - You should use a condom with spermicide even if you have had a vasectomy.
    - Keep using these birth control methods for 1 month after your last dose.
- ISTODAX may cause male infertility (low or no sperm count). This may affect your ability to father a child. Ask your healthcare professional for advice before starting treatment with ISTODAX.

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

Check-ups and Testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will do:

- Blood tests to check your liver, blood and heart health
- Electrocardiograms (ECGs) to check your heart beat

Driving cars and using machines: ISTODAX is known to cause fatigue and weakness. Avoid driving, using machines or doing hazardous tasks if you experience these side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ISTODAX:

- Medicines used to treat:
    - abnormal heart beats, such as: quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide, propafenone;
    - schizophrenia and other mental disorders, such as: chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone;
    - depression, such as: fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine, maprotiline, nefazodone;
    - bacterial infections, such as: erythromycin, clarithromycin, telithromycin, tacrolimus, moxifloxacin, levofloxacin, ciprofloxacin, rifampin, rifabutin, rifapentine;
    - HIV infections, such as: atazanavir, indinavir, nelfinavir, ritonavir, saquinavir;
    - fungal infections, such as: ketoconazole, fluconazole, voriconazole, itraconazole;
    - seizures, such as: phenytoin, carbamazepine, phenobarbital;
    - malaria, such as: quinine, chloroquine;
    - nausea, such as: dolasetron, ondansetron
    - cancer, such as: vandetanib, sunitinib, nilotinib, lapatinib, vorinostat
    - asthma, such as: salmeterol, formoterol
- Blood thinner medicine, like warfarin sodium;
- Birth control that contains estrogen, like birth control “pills”, patches, implants, or intrauterine devices (IUDs);
- St. John’s Wort (*Hypericum perforatum*), an herbal treatment for depression
- Dexamethasone, a steroid used to treat different inflammatory conditions, allergic reactions, skin diseases, eye problems, breathing problems, bowel disorders, cancer, and immune system disorders;
- Domperidone, used to treat gastrointestinal problems;
- Methadone, an opioid used for chronic pain relief;
- Any medicine that cause imbalance in the electrolytes in your body:
    - diuretics (water pills)
    - laxatives and enemas, used to treat constipation
    - amphotericin B, used to treat fungal infections
    - high dose corticosteroids, used to treat inflammation

This list might not be all of the drugs that may cause side effects during treatment with ISTODAX.

How to take ISTODAX:

- ISTODAX will be given to you by a healthcare professional as an intravenous (IV) injection into your vein. It is usually over 4 hours.
- ISTODAX is usually given on Day 1, Day 8, and Day 15 of a 28 day cycle of treatment.
- Your healthcare professional will decide for how long you will receive treatment with ISTODAX.

Usual dose:

- **Adults:** Your healthcare professional will choose the starting dose of ISTODAX that is right for you.

Your healthcare professional may interrupt or stop your treatment or reduce your dose. This may happen if you:

- experience side effects, or
- your disease has gotten worse.

Overdose:

If you think you, or a person you are caring for, have taken too much ISTODAX, contact a healthcare professional, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- ISTODAX needs to be given on fixed schedule. If you miss an appointment, call your healthcare professional for instructions.
- Your missed dose should be given as soon as possible unless it is within 5 days of the next dose.

What are possible side effects from using ISTODAX?

These are not all the possible side effects you may have when taking ISTODAX. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- nausea, diarrhea, constipation, and loss of appetite
- tiredness
- Swelling of your mouth, legs
- Stomach, mouth, joint, limb or back pain
- Decreased appetite
- Change in sense of taste
- Dehydration
- Night sweats
- Headache
- Dizziness
- Runny nose
- Weight loss
- Muscle spasms
- Anxiety, trouble sleeping, depression
- Dry skin, rash, itchy skin

ISTODAX may cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Pancytopenia, including neutropenia, leukopenia, anemia, thrombocytopenia (decreased red and white blood cells and platelets): low red blood cell count: paleness of the skin, fatigue, weakness, rapid heart rate, shortness of breath, pale skin; low white blood cell count: fever, and symptoms of infection such as cough, aches, pains and flu-like symptoms; low platelet count: bruising easily and bleeding from the gums or other sites, fatigue, weakness		✓	
Vomiting		✓	
COMMON			
Deep vein thrombosis or pulmonary embolism (blood clot in the deep veins of the leg or arm or lung): swelling, pain, arm or leg may be warm to the touch and may appear red, chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath		✓	
Electrocardiogram (ECG) changes (changes in the electrical activity of your heart seen on ECG) **or QTc prolongation (heart rhythm condition), increased heart rate:** Irregular or abnormal heart beats, chest pain, shortness of breath, dizziness, palpitations, fainting, seizures			✓
Infection, including pneumonia (lung infection), sepsis (blood infection), urinary tract infection: fever, significant fatigue, shortness of breath, cough, burning on urination, frequent urination, blood in urine, pain in the pelvis,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
strong smelling urine, cloudy urine little to no urine, flu-like symptoms, muscle aches, worsening skin problems, sweating and shaking chills, confusion, nausea, vomiting, low blood pressure, high or low body temperature, thick white patches in the mouth, tongue or on the throat, sore throat			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
Tumor lysis syndrome (caused by the rapid breakdown of cancer cells): lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- The healthcare professional will store at room temperature (15 to 30°C).
- Vials of ISTODAX and supplied diluent should be stored together in carton until use.
- Keep out of reach and sight of children.

If you want more information about ISTODAX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.bms.com/ca, or by calling 1-866-463-6267.

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