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NEW Indication Announcement for ISTODAX® (romidepsin) for injection.

Dear State Society,

Celgene Corporation is pleased to announce ISTODAX (romidepsin) for injection is now approved for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least 1 prior therapy. ISTODAX is also approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least 1 prior systemic therapy.

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

Dosing and Administration

The recommended dose of romidepsin 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. Treatment discontinuation or interruption with or without dose reduction to 10 mg/m² may be needed to manage adverse drug reactions.

Drug NDC and Coding

ISTODAX is supplied as a kit containing 1 single-use vial of 10 mg of romidepsin and 1 single-use vial of Diluent for romidepsin containing a 2 mL deliverable volume. The national drug code (NDC) for ISTODAX is **59572-983-01**. The HCPCS Code for ISTODAX is **J9315**.

Storage

ISTODAX kit must be stored at 20°C to 25°C, excursions permitted between 15°C and 30°C. (See USP Controlled Room Temperature.)

Patient Assistance for ISTODAX

For more information regarding patient assistance for ISTODAX, contact Celgene Patient Support® at 1-800-931-8691.

ISTODAX® (romidepsin) for injection is indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

ISTODAX® (romidepsin) for injection is indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

Important Safety Information

WARNINGS AND PRECAUTIONS:

- Treatment with ISTODAX has been associated with thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; therefore, monitor these hematological parameters during treatment with ISTODAX and modify the dose as necessary
- Serious and sometimes fatal infections have been reported during treatment and within 30 days after treatment with ISTODAX and the risk of life threatening infections may be higher in patients with a history of extensive or intensive chemotherapy
- Electrocardiographic (ECG) changes have been observed with ISTODAX
- In patients with congenital long QT syndrome, 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 monitoring electrolytes and ECGs at baseline and periodically during treatment
- Due to the risk of QT prolongation, ensure that potassium and magnesium are within the normal range before administration
- Tumor lysis syndrome has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden should be closely monitored and appropriate precautions taken, and treatment should be instituted as appropriate
- Based on its mechanism of action, ISTODAX may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus (Pregnancy Category D)
- ISTODAX binds to estrogen receptors. Advise women of childbearing potential that ISTODAX may reduce the effectiveness of estrogen-containing contraceptives

ADVERSE REACTIONS:

Peripheral T-Cell Lymphoma

The most common Grade 3/4 adverse reactions (>5%) regardless of causality in Study 3 (n=131) were thrombocytopenia (24%), neutropenia (20%), anemia (11%), asthenia/fatigue (8%), and leukopenia (6%), and in Study 4 (n=47) were neutropenia (47%), leukopenia (45%), thrombocytopenia (36%), anemia (28%), asthenia/fatigue (19%), pyrexia (17%), vomiting (9%), and nausea (6%).

Infections were the most common type of serious adverse event reported in Study 3 (n=131) and Study 4 (n=47). In Study 3, 25 patients (19%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections.

The most common adverse reactions regardless of causality in Study 3 (n=131) were nausea (59%), asthenia/fatigue (55%), thrombocytopenia (41%), vomiting (39%), diarrhea (36%), and pyrexia (35%), and in Study 4 (n=47) were asthenia/fatigue (77%), nausea (75%), thrombocytopenia (72%), neutropenia (66%), anemia (62%), leukopenia (55%), pyrexia (47%), anorexia (45%), vomiting (40%), constipation (40%), and diarrhea (36%).

Cutaneous T-Cell Lymphoma

The most common Grade 3/4 adverse reactions (>5%) regardless of causality in Study 1 (n=102) were infections (11%) and asthenia/fatigue (8%), and in Study 2 (n=83) were lymphopenia (37%), infections (33%), neutropenia (27%), leukopenia (22%), anemia (16%), asthenia/fatigue (14%), thrombocytopenia (14%), hypophosphatemia (10%), vomiting (10%), dermatitis/exfoliative dermatitis (8%), hypermagnesemia (8%), hyperuricemia (8%), hypocalcemia (6%), nausea (6%), and pruritus (6%).

Infections were the most common type of serious adverse event reported in both Study 1 (n=102) and Study 2 (n=83) with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection.

The most common adverse reactions regardless of causality in Study 1 (n=102) were nausea (56%), asthenia/fatigue (53%), infections (46%), vomiting (34%), and anorexia (23%) and in Study 2 (n=83) were nausea (86%), asthenia/fatigue (77%), anemia (72%), thrombocytopenia (65%), ECG ST-T wave changes (63%), neutropenia (57%), lymphopenia (57%), infections (54%), anorexia (54%), vomiting (52%), hypocalcemia (52%), hyperglycemia (51%), hypoalbuminemia (48%), leukopenia (46%), dysgeusia (40%), and constipation (39%).

DRUG INTERACTIONS:

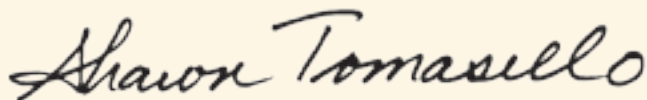
- ISTODAX is metabolized by CYP3A4. Avoid concomitant use with strong CYP3A4 inhibitors and potent CYP3A4 inducers if possible
- Caution should also be exercised with concomitant use of moderate CYP3A4 inhibitors and P-glycoprotein (P-gp, ABCB1) inhibitors
- Physicians should carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX and warfarin sodium derivatives

USE IN SPECIFIC POPULATIONS:

- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother
- Patients with moderate and severe hepatic impairment and/or patients with end-stage renal disease should be treated with caution

Please see accompanying full Prescribing Information, including WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.

Sincerely,



Shawn Tomasello
Corporate Vice President and General Manager,
US Hematology & Oncology
Celgene Corporation

