Indications for ISTODAX® (romidepsin) for injection

- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy
- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.
ISTODAX® (romidepsin) for injection is indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

### DOSING SCHEDULE

ISTODAX is administered once a week for 3 weeks—with 1 week off each dosing cycle

- 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
- Advise patients of the risk of tumor lysis syndrome (especially those with advanced stage disease and/or high tumor burden) to maintain high fluid intake for at least 72 hours after each dose

#### ONLY 3 DOSES EVERY 28 DAYS

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<td>Day 8</td>
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</table>

ISTODAX is supplied as a kit which includes a 10 mg single-dose vial of ISTODAX and one single-dose vial with 2.2 mL (deliverable volume) of diluent.

Cycles should be repeated every 28 days provided the patient continues to benefit from and tolerates the treatment.

### WARNINGS AND PRECAUTIONS

- **Myelosuppression:** ISTODAX® (romidepsin) can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts regularly during treatment with ISTODAX; interrupt and/or modify the dose as necessary
- **Infections:** Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported during and within 30 days after treatment with ISTODAX in clinical trials. The risk of life threatening infections may be greater 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. Reactivation of Epstein Barr viral infection led to liver failure. Consider monitoring for reactivation and antiviral prophylaxis in patients with evidence of prior hepatitis B infection. Ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation in one case

Please see Important Safety Information on pages 10-11 and accompanying Full Prescribing Information.

### DOSING MODIFICATIONS

#### NONHEMATOLOGIC TOXICITIES (EXCEPT ALOPECIA)²

- Delay dose until toxicity returns to ≤Grade 1 or baseline, then therapy may be restarted at 14 mg/m²
- Delay dose until toxicity returns to ≤Grade 1 or baseline, then therapy should be permanently reduced to 10 mg/m²

#### HEMATOLOGIC TOXICITIES¹

- Delay treatment until the ANC returns to ≥1.5 x 10⁹/L or baseline, then therapy may be restarted at 14 mg/m²
- Delay treatment until platelets return to ≥75 x 10⁹/L or baseline, then therapy may be restarted at 14 mg/m²
- Delay dose until the specific cytopenia returns to ≤Grade 1 or baseline, then therapy should be permanently reduced to 10 mg/m²

#### DISCONTINATIONS

- **CTCL**
  - Discontinuation due to an adverse event occurred in 21% of patients in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of patients in either study included infection, fatigue, dyspnea, QT prolongation, and hypomagnesemia.
- **PTCL**
  - Discontinuation due to an adverse event occurred in 19% of patients in Study 3 and in 28% of patients in Study 4. In Study 3, thrombocytopenia and pneumonia were the only events leading to treatment discontinuation in at least 2% of patients. In Study 4, events leading to treatment discontinuation in ≥2 patients were thrombocytopenia (11%), anemia, infection, and alanine aminotransferase increased (4%).

Patients stayed on ISTODAX for a mean duration of 5.6 months in both CTCL studies and PTCL Study 3. The mean duration was 9.6 months in PTCL Study 4.
ISTODAX® (romidepsin) for injection is indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

**PRIOR TO ADMINISTRATION**

### Important Factors to Consider

| MYELOSUPPRESSION | Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia
|                  | Monitor blood counts regularly during treatment with ISTODAX, and modify the dose as necessary

| INFECTION | Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported in clinical trials with ISTODAX
|           | These can occur during treatment and within 30 days after treatment
|           | The risk of life threatening infections may be greater 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
|           | Reactivation of hepatitis B virus infection has occurred in 1% of PTCL patients in clinical trials in Western populations
|           | In patients with evidence of prior hepatitis B infection, consider monitoring for reactivation, and consider antiviral prophylaxis. Reactivation of Epstein Barr viral infection leading to liver failure has occurred in a trial of patients with relapsed or refractory extranodal NK/T-cell lymphoma
|           | In one case, ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation

| ECG | Electrocardiographic (ECG) changes have been observed
|     | - Congenital long QT syndrome
|     | - A history of significant cardiovascular disease
|     | - Patients taking antiarrhythmic medicines or medicinal products that lead to significant QT prolongation
|     | Confirm that potassium and magnesium levels are within normal range before administration of ISTODAX

| PREGNANCY | ISTODAX may cause fetal harm when administered to a pregnant woman
|           | Advise women of potential hazard to the fetus and to avoid pregnancy while receiving ISTODAX

| HEPATIC IMPAIRMENT | No dedicated hepatic impairment study for ISTODAX has been conducted
|                   | Mild hepatic impairment does not alter pharmacokinetics of romidepsin based on a population pharmacokinetic analysis. Patients with moderate and severe hepatic impairment should be treated with caution

| RENAL IMPAIRMENT | No dedicated renal impairment study for ISTODAX has been conducted
|                  | Based upon the population pharmacokinetic analysis, renal impairment is not expected to significantly influence drug exposure
|                  | 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

| EMETOGENIC POTENTIAL | Nausea and vomiting are common following treatment with ISTODAX
|                    | Prophylactic antiemetics are recommended for all patients

### WARNINGS AND PRECAUTIONS (cont.)

- Tumor lysis syndrome: TLS (Tumor lysis syndrome) has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden are at greater risk and should be closely monitored and managed as appropriate

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**ISTODAX**

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**PRIOR TO ADMINISTRATION**

### Important Factors to Consider

| METABOLISM | ISTODAX undergoes extensive metabolism in vitro primarily by CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19
|            | When coadministering ISTODAX with strong CYP3A4 inhibitors, patients should be monitored for toxicities related to increased ISTODAX exposure
|            | Avoid use with rifampin and strong CYP3A4 inducers

| DRUG INTERACTIONS | Warfarin or Coumarin Derivatives
|                  | - Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin. Although the interaction potential between ISTODAX and warfarin has not been formally studied, monitor PT and INR more frequently in patients concurrently receiving ISTODAX and warfarin
|                  | Drugs that Inhibit Cytochrome P450 3A4 Enzymes
|                  | - Romidepsin is metabolized by CYP3A4. Strong CYP3A4 inhibitors increase concentrations of romidepsin. In a pharmacokinetic drug interaction trial the strong CYP3A4 inhibitor ketocazole increased romidepsin (AUC, ___) by approximately 25%
|                  | - Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity when romidepsin is initially co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nefilavir, ritonavir, saquinavir, telithromycin, voriconazole)
|                  | Drugs that Induce Cytochrome P450 3A4 Enzymes
|                  | - Avoid use with rifampin and strong CYP3A4 inducers
|                  | ISTODAX 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

### 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 (19%), 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, 26 patients (20%) 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 (44%), 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%).
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.

This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

### Dosing Examples

ISTODAX is supplied as a kit which includes a 10 mg single-dose vial of ISTODAX and one single-dose vial containing 2.2 mL (deliverable volume) of diluent.

#### Dosing Examples Based on Patient’s Height and Weight (BSA)

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>BSA</th>
<th>DOSAGE</th>
<th>APPROXIMATE NUMBER OF VIALS NEEDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark</td>
<td>Age: 68</td>
<td>Height: 75”</td>
<td>Weight: 200 lb BSA: 2.19 m²</td>
</tr>
<tr>
<td>Ellen</td>
<td>Age: 63</td>
<td>Height: 63”</td>
<td>Weight: 124 lb BSA: 1.58 m²</td>
</tr>
<tr>
<td>Tom</td>
<td>Age: 72</td>
<td>Height: 68”</td>
<td>Weight: 150 lb BSA: 1.81 m²</td>
</tr>
</tbody>
</table>

*Discard any unused portion of the reconstituted ISTODAX solution. BSA=body surface area.

### Counseling & Dosing Examples

### ADVERSE REACTIONS

**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 (22%), 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.

**Peripheral T-Cell Lymphoma (cont.)**

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%).

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

This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

### Patients should be instructed to read the patient insert carefully

Please see Important Safety Information on pages 10-11 and accompanying Full Prescribing Information.
**ADMINISTRATION**

Extract the appropriate amount of ISTODAX from the vials to deliver the desired dose, using proper aseptic technique

- ISTODAX must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion
- ISTODAX and diluent vials contain an overfill to ensure the recommended volume can be withdrawn at a concentration of 5 mg/mL
- Infuse over 4 hours
- 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

**ADVERSE REACTIONS**

- Cutaneous T-Cell Lymphoma (cont.)
  - 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%).

**USE IN SPECIFIC POPULATIONS**

- Pregnancy Category D: 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
- 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

**ISTODAX (romidepsin) for injection is indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.**

**ADMINISTRATION**

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

- ISTODAX is a cytotoxic drug. Use appropriate handling procedures

Please refer to the accompanying Reconstitution Flashcard and Prescribing Information for reconstitution instructions

Please see Important Safety Information on pages 10-11 and accompanying Full Prescribing Information.
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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

- **Myelosuppression:** ISTODAX® (romidepsin) can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts regularly during treatment with ISTODAX; interrupt and/or modify the dose as necessary
- **Infections:** Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported during and within 30 days after treatment with ISTODAX in clinical trials. The risk of life-threatening infections may be greater 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. Reactivation of Epstein Barr viral infection led to liver failure. Consider monitoring for reactivation and antiviral prophylaxis in patients with evidence of prior hepatitis B infection. Ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation in one case
- **Electrocardiographic (ECG) changes:** ECG changes have been observed with 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, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment. Confirm that potassium and magnesium levels are within the normal range before administration of ISTODAX
- **Tumor lysis syndrome:** TLS (Tumor lysis syndrome) has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden are at greater risk and should be closely monitored and managed as appropriate
- **Embryo-fetal toxicity:** ISTODAX may cause fetal harm when administered to a pregnant woman. Advise women of potential hazard to the fetus and to avoid pregnancy while receiving ISTODAX

**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, 28 patients (21%) 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%).

**Dosage and Administration**

ISTODAX® (romidepsin) is administered once a week for 3 weeks—with 1 week off each dosing cycle.

**DRUG INTERACTIONS**

- **Drug-drug interactions:** Monitor patients for toxicity related to increased romidepsin exposure and follow dose modifications for toxicity when ISTODAX is initially co-administered with strong CYP3A4 inhibitors

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy Category D:** 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
- **Breastfeeding:** It is unknown if romidepsin is 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
- **Liver impairment:** Patients with decompensated liver impairment should be treated with caution

**STORAGE AND STABILITY**

ISTODAX is supplied as a kit that contains a 10 mg single-dose vial of ISTODAX and 10 mL of 0.9% Sodium Chloride sterile diluent. The vials of ISTODAX and diluent are stable in the vial if stored in their respective containers at room temperature (20° to 25°C [68° to 77°F]) recommended as 20° to 25°C (68° to 77°F). However it should be administered as stable in the vial

**Recommended Use**

ISTODAX® (romidepsin) is recommended as 20° to 25°C (68° to 77°F). However it should be administered as

**Stability**

ISTODAX® (romidepsin) is stable in the vial when stored at room temperature (20° to 25°C [68° to 77°F]) recommended as 20° to 25°C (68° to 77°F). However it should be administered as

**Compatibility**

ISTODAX® (romidepsin) should be administered in a single 4-hour period into a 500 mL of 0.9% Sodium Chloride solution, the diluted solution is chemically stable in the vial

**Compatibility of CYP3A4 inhibitors**

- **CYP3A4 inhibitors:** Monitor patients for toxicity related to increased romidepsin exposure and follow dose modifications for toxicity when ISTODAX is initially co-administered with strong CYP3A4 inhibitors

**Use in Renal Impairment**

**Stability**

ISTODAX® (romidepsin) for injection is supplied as a kit that contains

**Storage**

ISTODAX® (romidepsin) for injection is supplied as a kit that contains

**Please see accompanying Full Prescribing Information.**

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STORAGE AND STABILITY

ISTODAX® (romidepsin) for injection is supplied as a kit that contains

- Two vials in a single carton. The carton must be stored at 20° to 25°C (68° to 77°F), excursions permitted between 15°C to 30°C (between 59° and 86°F).

**Important Stability Considerations**

<table>
<thead>
<tr>
<th>Unopened vial</th>
<th>Reconstituted solution in the vial</th>
<th>The solution after dilution in 0.9% Sodium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The carton containing unopened vials of ISTODAX and diluent must be stored at room temperature recommended as 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (between 59° and 86°F)</td>
<td>- Once diluent is added to the lyophilized powder, the reconstituted ISTODAX solution is chemically stable in the vial for up to 8 hours at room temperature recommended as 20° to 25°C (68° to 77°F)</td>
<td>- Once the reconstituted ISTODAX solution is further diluted in 500 mL of 0.9% Sodium Chloride, the diluted solution is chemically stable for up to 24 hours at room temperature recommended as 20° to 25°C (68° to 77°F). However it should be administered as soon after dilution as possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles</td>
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<td></td>
<td></td>
<td>- Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit</td>
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<tr>
<td></td>
<td></td>
<td>- Refer to institutional guidelines for preparation and administration of cytotoxic drugs</td>
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</tbody>
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Please see Important Safety Information on pages 10-11 and accompanying Full Prescribing Information.