NAME OF THE MEDICINAL PRODUCT

ISTODAX

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each kit contains:
1 vial contains 10 mg of romidepsin
1 vial contains 2.2 ml of diluent

PHARMACEUTICAL FORM

Please refer to section 3

1 INDICATIONS AND USAGE

1.1 Cutaneous T-Cell Lymphoma

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

1.2 Peripheral T-Cell Lymphoma

ISTODAX is indicated for treatment of peripheral T-cell lymphoma (PTCL) in adult 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of romidepsin 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 drug.

2.2 Dose Modification

Nonhematologic toxicities except alopecia

- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to Grade 0-1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to Grade 0-1 or baseline and the dose should be permanently reduced to 10 mg/m^2.
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2.
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC greater than or equal to 1.5×10^9/L and platelet count greater than or equal to 75×10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (greater than or equal to 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to less than or equal to Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m^2.

2.3 Dosage in Patients with 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)

• 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/m2 (50% reduction)

• 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)

2.4 Instructions for Preparation and Intravenous Administration

ISTODAX is a cytotoxic drug. Use appropriate handling procedures.

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.

- Each 10 mg single-dose vial of ISTODAX must be reconstituted with 2.2 mL of the supplied diluent.
- With a suitable syringe, aseptically withdraw 2.2 mL from the supplied diluent vial, and slowly inject it into the ISTODAX (romidepsin) for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain ISTODAX 5 mg/mL. The reconstituted ISTODAX vial will contain 2 mL of deliverable volume of drug product. The reconstituted ISTODAX solution is chemically stable for up to 8 hours at room temperature.
- Extract the appropriate amount of ISTODAX from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute ISTODAX in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

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.

3 DOSAGE FORMS AND STRENGTHS

ISTODAX is supplied as a kit which includes a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin, 22 mg of the bulking agent, povidone, USP, and hydrochloric acid, NF, as a pH adjuster. In addition, each kit includes a single-dose sterile vial containing 2.4 mL (2.2 mL deliverable volume) of the diluent composed of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 3.

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.2 Infections

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 *[see Adverse Reactions (6.1)]*.

Reactivation of hepatitis B virus infection has occurred in 1% of PTCL patients in clinical trials in Western populations *[see Adverse Reactions (6.1)]*. 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.

5.3 Electrocardiographic Changes

Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown *[see Adverse Reactions (6.1)]*.

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 normal range before administration of ISTODAX *[see Adverse Reactions (6.1)]*.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden are at greater risk, should be closely monitored, and managed as appropriate.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, ISTODAX can cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and caused adverse developmental outcomes at exposures below those in patients at the recommended dose of 14 mg/m^2. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Advise males with female sexual partners of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (11.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the prescribing information.

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Electrocardiographic Changes *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

Cutaneous T-Cell Lymphoma

The safety of ISTODAX was evaluated in 185 patients with CTCL in 2 single arm clinical studies in which patients received a starting dose of 14 mg/m^2. The mean duration of treatment in these studies was 5.6 months (range: <1 to 83.4 months).

Common Adverse Reactions

Table 1 summarizes the most frequent adverse reactions (>20%) regardless of causality using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0). Due to methodological differences between the studies, the AE data are presented separately for Study 1 and Study 2. Adverse reactions are ranked by their incidence in Study 1. Laboratory abnormalities commonly reported (>20%) as adverse reactions are included in Table 1.

Table 1. Adverse Reactions Occurring in >20% of Patients in Either CTCL Study (N=185)

	Study 1 (n=102)		Study 2 (n=83)	
Adverse Reactions n (%)	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Any adverse reactions	*99 (97)*	*36 (35)*	*83 (100)*	*68 (82)*
Nausea	57 (56)	3 (3)	71 (86)	5 (6)
Asthenia/Fatigue	54 (53)	8 (8)	64 (77)	12 (14)
Infections	47 (46)	11 (11)	45 (54)	27 (33)
Vomiting	35 (34)	1 (<1)	43 (52)	8 (10)
Anorexia	23 (23)	1 (<1)	45 (54)	3 (4)
Hypomagnesemia	22 (22)	1 (<1)	23 (28)	0
Diarrhea	20 (20)	1 (<1)	22 (27)	1 (1)
Pyrexia	20 (20)	4 (4)	19 (23)	1 (1)
Anemia	19 (19)	3 (3)	60 (72)	13 (16)
Thrombocytopenia	17 (17)	0	54 (65)	12 (14)
Dysgeusia	15 (15)	0	33 (40)	0
Constipation	12 (12)	2 (2)	32 (39)	1 (1)
Neutropenia	11 (11)	4 (4)	47 (57)	22 (27)
Hypotension	7 (7)	3 (3)	19 (23)	3 (4)
Pruritus	7 (7)	0	26 (31)	5 (6)
Hypokalemia	6 (6)	0	17 (20)	2 (2)
Dermatitis/Exfoliative dermatitis	4 (4)	1 (<1)	22 (27)	7 (8)
Hypocalcemia	4 (4)	0	43 (52)	5 (6)
Leukopenia	4 (4)	0	38 (46)	18 (22)
Lymphopenia	4 (4)	0	47 (57)	31 (37)
Alanine aminotransferase increased	3 (3)	0	18 (22)	2 (2)
Aspartate aminotransferase increased	3 (3)	0	23 (28)	3 (4)
Hypoalbuminemia	3 (3)	1 (<1)	40 (48)	3 (4)
Electrocardiogram ST-T wave changes	2 (2)	0	52 (63)	0
Hyperglycemia	2 (2)	2 (2)	42 (51)	1 (1)
Hyponatremia	1 (<1)	1 (<1)	17 (20)	2 (2)
Hypermagnesemia	0	0	22 (27)	7 (8)
Hypophosphatemia	0	0	22 (27)	8 (10)
Hyperuricemia	0	0	27 (33)	7 (8)

Serious Adverse Reactions

Infections were the most common type of SAE reported in both studies with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection. Serious adverse reactions reported in >2% of patients in Study 1 were sepsis and pyrexia (3%). In Study 2, serious adverse reactions in >2% of patients were fatigue (7%), supraventricular arrhythmia, central line infection, neutropenia (6%), hypotension, hyperuricemia, edema (5%), ventricular arrhythmia, thrombocytopenia, nausea, leukopenia, dehydration, pyrexia, aspartate aminotransferase increased, sepsis, catheter related infection, hypophosphatemia and dyspnea (4%).

There were eight deaths not due to disease progression. In Study 1, there were two deaths: one due to cardiopulmonary failure and one due to acute renal failure. There were six deaths in Study 2: four due to infection , and one each due to myocardial ischemia and acute respiratory distress syndrome.

Discontinuations

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.

Peripheral T-Cell Lymphoma

The safety of ISTODAX was evaluated in 178 patients with PTCL in a sponsor-conducted pivotal study (Study 3) and a secondary NCI-sponsored study (Study 4) in which patients received a starting dose of 14 mg/m^2. The mean duration of treatment and number of cycles were 5.6 months and 6 cycles in Study 3 and 9.6 months and 8 cycles in Study 4.

Common Adverse Reactions

Table 2 summarizes the most frequent adverse reactions (≥10%) regardless of causality, using the NCI-CTCAE, Version 3.0. The AE data are presented separately for Study 3 and Study 4. Laboratory abnormalities commonly reported (≥10%) as adverse reactions are included in Table 2.

Table 2. Adverse Reactions Occurring in ≥10% of Patients with PTCL in Study 3 and Corresponding Incidence in Study 4 (N=178)

	Study 3 (N=131)		Study 4 (N=47)	
Adverse Reactions n (%)	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Any adverse reactions	*128 (97)*	*88 (67)*	*47 (100)*	*40 (85)*
Gastrointestinal disorders				
Nausea	77 (59)	3 (2)	35 (75)	3 (6)
Vomiting	51 (39)	6 (5)	19 (40)	4 (9)
Diarrhea	47 (36)	3 (2)	17 (36)	1 (2)
Constipation	39 (30)	1 (<1)	19 (40)	1 (2)
Abdominal pain	18 (14)	3 (2)	6 (13)	1 (2)
Stomatitis	14 (11)	0	3 (6)	0
General disorders and administration site conditions				
Asthenia/Fatigue	72 (55)	11 (8)	36 (77)	9 (19)
Pyrexia	46 (35)	8 (6)	22 (47)	8 (17)
Chills	14 (11)	1 (<1)	8 (17)	0
Edema peripheral	13 (10)	1 (<1)	3 (6)	0
Blood and lymphatic system disorders				
Thrombocytopenia	53 (41)	32 (24)	34 (72)	17 (36)
Neutropenia	39 (30)	26 (20)	31 (66)	22 (47)
Anemia	33 (25)	14 (11)	29 (62)	13 (28)
Leukopenia	16 (12)	8 (6)	26 (55)	21 (45)
Metabolism and nutrition disorders				
Anorexia	37 (28)	2 (2)	21 (45)	1 (2)
Hypokalemia	14 (11)	3 (2)	8 (17)	1 (2)
Nervous system disorders				
Dysgeusia	27 (21)	0	13 (28)	0
Headache	19 (15)	0	16 (34)	1 (2)
Respiratory, thoracic and mediastinal disorders				
Cough	23 (18)	0	10 (21)	0
Dyspnea	17 (13)	3 (2)	10 (21)	2 (4)
Investigations				
Weight decreased	14 (11)	0	7 (15)	0
Cardiac disorders				
Tachycardia	13 (10)	0	0	0

Serious Adverse Reactions

Infections were the most common type of SAE reported. In Study 3, twenty-six patients (20%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, eleven patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections. Serious adverse reactions reported in ≥2% of patients in Study 3 were pyrexia (8%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis, (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnea, and dehydration (2%). In Study 4, serious adverse reactions in ≥2 patients were pyrexia (17%), aspartate aminotransferase increased, hypotension (13%), anemia, thrombocytopenia, alanine aminotransferase increased (11%), infection, dehydration, dyspnea (9%), lymphopenia, neutropenia, hyperbilirubinemia, hypocalcemia, hypoxia (6%), febrile neutropenia, leukopenia, ventricular arrhythmia, vomiting, hypersensitivity, catheter related infection, hyperuricemia, hypoalbuminemia, syncope, pneumonitis, packed red blood cell transfusion, and platelet transfusion (4%).

Reactivation of hepatitis B virus infection has occurred in 1% of patients with PTCL in clinical trials in Western populations enrolled in Study 3 and Study 4 *[see Warnings and Precautions (5.2)]*.

Deaths due to all causes within 30 days of the last dose of ISTODAX occurred in 7% of patients in Study 3 and 17% of patients in Study 4. In Study 3, there were 5 deaths unrelated to disease progression that were due to infections, including multi-organ failure/sepsis, pneumonia, septic shock, candida sepsis, and sepsis/cardiogenic shock. In Study 4, there were 3 deaths unrelated to disease progression that were due to sepsis, aspartate aminotransferase elevation in the setting of Epstein Barr virus reactivation, and death of unknown cause.

Discontinuations

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%).

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il /and emailed to the Registration Holder’s Patient Safety Unit at: drugsafety@neopharmgroup.com

7 DRUG INTERACTIONS

7.1 Warfarin or Coumarin Derivatives

Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin. Monitor PT and INR more frequently in patients concurrently receiving ISTODAX and warfarin *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit CYP3A4 Enzymes

Strong CYP3A4 inhibitors increase concentrations of romidepsin. *[see Clinical Pharmacology (12.3)]*. Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity [see Dosage and Administration (2.2)] when ISTODAX is initially co-administered with strong CYP3A4 inhibitors

7.3 Drugs That Induce CYP3A4 Enzymes

Rifampin (a potent CYP3A4 inducer) increased the concentrations of romidepsin [see Clinical Pharmacology (12.3)]. Avoid co-administration of ISTODAX with rifampin.

The use of other potent CYP3A4 inducers should be avoided when possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings from animal studies, ISTODAX can cause embryo-fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*.

There are no available data on ISTODAX use in pregnant women to inform a drug associated risk of major birth defects and miscarriage. In an animal reproductive study, romidepsin was embryocidal and caused adverse developmental outcomes including embryo-fetal toxicity and malformations at exposures below those in patients at the recommended dose *(see Data)*. Advise pregnant women of the potential risk to a fetus and to avoid becoming pregnant while receiving ISTODAX, and for at least 1 month after the last dose.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Data

Animal Data
Romidepsin was administered intravenously to pregnant rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or postimplantation loss was observed at the high-dose of 0.5 mg/kg/day, a maternally toxic dose. Adverse embryo-fetal effects were noted at romidepsin doses of ≥0.1 mg/kg/day, with systemic exposures (AUC) ≥0.2% of the human exposure at the recommended dose of 14 mg/m^2/week. Drug-related fetal effects consisted of reduced fetal body weights, folded retina, rotated limbs, and incomplete sternal ossification.

8.2 Lactation

Risk Summary

There are no data on the presence of ISTODAX or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the breastfed child, advise lactating women not to breastfeed during treatment with ISTODAX and for at least 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

ISTODAX can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Perform pregnancy testing in females of reproductive potential within 7 days prior to initiating therapy with ISTODAX.
Contraception

Females
Advise females of reproductive potential to use effective contraception during treatment with ISTODAX and for at least 1 month after the last dose. ISTODAX may reduce the effectiveness of estrogen-containing contraceptives. Therefore, alternative methods of non-estrogen containing contraception (e.g., condoms, intrauterine devices) should be used in patients receiving ISTODAX.

Males
Advise males with female partners of reproductive potential to use effective contraception and to avoid fathering a child during treatment with ISTODAX and for at least 1 month after the last dose.
Infertility

Based on findings in animals, romidepsin has the potential to affect male and female fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the approximately 300 patients with CTCL or PTCL in trials, about 25% were >65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

In a hepatic impairment study, ISTODAX was evaluated in 19 patients with advanced cancer and mild (8), moderate (5), or severe (6) hepatic impairment There were 4 deaths during the first cycle of treatment: 1 patient with mild hepatic impairment 1 patient with moderate hepatic impairment, and 2 patients with severe hepatic

Impairment. The use of ISTODAX is not recommended in patients with severe hepatic impairment. No dose adjustments are recommended for patients with mild hepatic impairment. Reduce the ISTODAX starting dose for patients with moderate hepatic impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)]*. Monitor patients with hepatic impairment more frequently for toxicity, especially during the first cycle of therapy.

9 OVERDOSAGE

No specific information is available on the treatment of overdosage of ISTODAX.

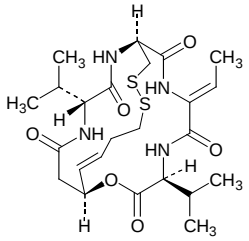
Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2-fold the recommended human dose based on the body surface area, included irregular respiration, irregular heartbeat, staggering gait, tremor, and tonic convulsions.

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 ISTODAX and it is not known if ISTODAX is dialyzable.

10 DESCRIPTION

Romidepsin, a histone deacetylase (HDAC) inhibitor, is a bicyclic depsipeptide. At room temperature, romidepsin is a white powder and is described chemically as (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. The empirical formula is $C_{24}H_{36}N_4O_6S_2$.

The molecular weight is 540.71 and the structural formula is:



ISTODAX (romidepsin) for injection is intended for intravenous infusion only after reconstitution with the supplied diluent and after further dilution with 0.9% Sodium Chloride, USP.

ISTODAX is supplied as a kit containing 2 vials.

ISTODAX (romidepsin) for injection is a sterile lyophilized white powder and is supplied in a 10 mg single-dose vial containing 11 mg romidepsin and 22 mg povidone, USP, and hydrochloric acid, NF, as a pH adjuster..

Diluent for ISTODAX is a sterile clear solution and is supplied in a single-dose vial containing 2.4 mL (2.2 mL deliverable volume). Diluent for ISTODAX contains 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP.

11 CLINICAL PHARMACOLOGY

11.1 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 with IC_{50} values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

11.2 Pharmacodynamics

Cardiac Electrophysiology

At doses of 14 mg/m^2 as a 4-hour intravenous infusion, and at doses of 8 (0.57 times the recommended dose), 10 (0.71 times the recommended dose) or 12 (0.86 times the recommended dose) mg/m^2 as a 1-hour infusion, no large changes in the mean QTc interval (>20 milliseconds) from baseline based on Fridericia correction method were detected. Small increase in mean QT interval (< 10 milliseconds) and mean QT interval increase between 10 to 20 milliseconds cannot be excluded.

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 20 beats per minute occurring at the 6-hour time point after start of romidepsin infusion for patients receiving 14 mg/m^2 as a 4-hour infusion.

11.3 Pharmacokinetics

In patients with T-cell lymphomas who received 14 mg/m^2 of romidepsin intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle, geometric mean values of the maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve ($AUC_{0-\infty}$) were 377 ng/mL and 1549 ng*hr/mL, respectively. Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 (0.07 times the recommended dose) to 24.9 (1.76 times the recommended dose) mg/m^2 when administered intravenously over 4 hours in patients with advanced cancers.

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 efflux transporter P-glycoprotein (P-gp, ABCB1).

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.

Excretion

Following 4-hour intravenous administration of romidepsin at 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle in patients with T-cell lymphomas, the terminal half-life ($t_{1/2}$) was approximately 3 hours. No accumulation of plasma concentration of romidepsin was observed after repeated dosing.

Drug Interactions

Ketoconazole: Following co-administration of 8 mg/m^2 ISTODAX (4-hour infusion) with ketoconazole, the overall romidepsin exposure was increased by approximately 25% and 10% for $AUC_{0-\infty}$ and C_{max}, respectively, compared to romidepsin alone, and the difference in $AUC_{0-\infty}$ between the 2 treatments was statistically significant.

Rifampin: Following co-administration of 14 mg/m^2 ISTODAX (4-hour infusion) with rifampin, the overall romidepsin exposure was increased by approximately 80% and 60% for $AUC_{0-\infty}$ and C_{max}, respectively, compared to romidepsin alone, and the difference between the 2 treatments was statistically significant. Co-administration of rifampin decreased the romidepsin clearance and volume of distribution by 44% and 52%, respectively. The increase in exposure seen after co-administration with rifampin is likely due to rifampin's inhibition of an undetermined hepatic uptake process that is predominant for the disposition of ISTODAX.

Drugs that inhibit P-glycoprotein: Drugs that inhibit p-glycoprotein may increase the concentration of romidepsin.

Specific Populations

Effect of Age, Gender, Race or Renal Impairment

The pharmacokinetics of romidepsin was not influenced by age (27 to 83 yrs), gender, race (white vs. black) or 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 (estimated creatine clearance less than 15 mL/min) on romidepsin pharmacokinetics has not been studied.

Hepatic Impairment

Romidepsin clearance decreased with increased severity of hepatic impairment. In patients with cancer, the geometric mean C_{max} values after administration of 14, 7, and 5 mg/m^2 romidepsin in patients with mild (B1: bilirubin ≤ULN and AST >ULN; B2: bilirubin >ULN but ≤1.5 x ULN and any AST), moderate (bilirubin >1.5 x ULN to ≤3 x ULN and any AST), and severe (bilirubin >3 x ULN and any AST) hepatic impairment were approximately 111%, 96%, and 86% of the corresponding value after administration of 14 mg/m^2 romidepsin in patients with normal (bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ULN) hepatic function, respectively. The geometric mean AUC_{inf} values in patients with mild, moderate, and severe hepatic impairment were approximately 144%, 114%, and 116% of the corresponding value in patients with normal hepatic function, respectively. Among these 4 cohorts, moderate interpatient variability was noted for the exposure parameters Cmax and AUC_{inf}, as the coefficient of variation (CV) ranged from 30% to 54%.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with romidepsin. Romidepsin was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. 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.

Based on nonclinical findings, male and female fertility may be compromised by treatment with ISTODAX. In a 26-week toxicology study, romidepsin administration resulted in testicular degeneration in rats at 0.33 mg/kg/dose (2 mg/m^2/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0-\infty}$ values that were approximately 2% the exposure level in patients receiving the recommended dose of 14 mg/m^2/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and prostate organ weights were decreased in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m^2/day), approximately 30% the estimated human daily dose based on body surface area. Romidepsin showed high affinity for binding to estrogen receptors in pharmacology studies. In a 26-week toxicology study in rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females administered doses as low as 0.1 mg/kg/dose (0.6 mg/m^2/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0-\infty}$ values that were 0.3% of those in patients receiving the recommended dose of 14 mg/m^2/dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were observed in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m^2/day). This dose is approximately 30% the estimated human daily dose based on body surface area.

13 CLINICAL STUDIES

13.1 Cutaneous T-Cell Lymphoma

ISTODAX was evaluated in 2 multicenter, single-arm clinical studies in patients with CTCL. Overall, 167 patients with CTCL were treated in the US, Europe, and Australia. Study 1 included 96 patients with confirmed CTCL after failure of at least 1 prior systemic therapy. Study 2 included 71 patients with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. Patients were treated with ISTODAX at a starting dose of 14 mg/m^2 infused over 4 hours on days 1, 8, and 15 every 28 days.

In both studies, patients could be treated until disease progression at the discretion of the investigator and local regulators. Objective disease response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and abnormal circulating T-cells ("Sézary cells").

The primary efficacy endpoint for both studies was overall objective disease response rate (ORR) based on the investigator assessments, and defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as ≥ 50% improvement in disease. Secondary endpoints in both studies included duration of response and time to response.

Baseline Patient Characteristics

Demographic and disease characteristics of the patients in Study 1 and Study 2 are provided in Table 3.

Table 3. Baseline Patient Characteristics (CTCL Population)

Characteristic	Study 1 (N=96)	Study 2 (N=71)
Age		
N	96	71
Mean (SD)	57 (12)	56 (13)
Median (Range)	57 (21, 89)	57 (28, 84)
Sex, n (%)		
Men	59 (61)	48 (68)
Women	37 (39)	23 (32)
Race, n (%)		
White	90 (94)	55 (77)
Black	5 (5)	15 (21)
Other/Not Reported	1 (1)	1 (1)
Stage of Disease at Study Entry, n (%)		
IA	0 (0)	1 (1)
IB	15 (16)	6 (9)
IIA	13 (14)	2 (3)
IIB	21 (22)	14 (20)
III	23 (24)	9 (13)
IVA	24 (25)	27 (38)
IVB	0 (0)	12 (17)
Number of Prior Skin-Directed Therapies		
Median (Range)	2 (0, 6)	1 (0, 3)
Number of Prior Systemic Therapies		
Median (Range)	2 (1, 8)	2 (0, 7)

Clinical Results

Efficacy outcomes for CTCL patients are provided in Table 4. Median time to first response was 2 months (range 1 to 6) in both studies. Median time to CR was 4 months in Study 1 and 6 months in Study 2 (range 2 to 9).

Table 4. Clinical Results for CTCL Patients

Response Rate	Study 1 (N=96)	Study 2 (N=71)
ORR (CR + PR), n (%) [95% Confidence Interval]	33 (34) [25, 45]	25 (35) [25, 49]
CR, n (%) [95% Confidence Interval]	6 (6) [2, 13]	4 (6) [2, 14]
PR, n (%) [95% Confidence Interval]	27 (28) [19, 38]	21 (30) [20, 43]
Duration of Response (months)		
N	33	25
Median (range)	15 (1, 20*)	11 (1, 66*)

*Denotes censored value

13.2 Peripheral T-Cell Lymphoma

ISTODAX was evaluated in a multicenter, single-arm, international clinical study in patients with PTCL who had failed at least 1 prior systemic therapy (Study 3). Patients in US, Europe, and Australia 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; patients who developed progressive disease (PD), significant toxicity, or who met another criterion for study termination were to discontinue treatment. Responding patients had the option of continuing treatment beyond 6 cycles at the discretion of the patient and Investigator until study withdrawal criteria were met.

Primary assessment of efficacy was based on rate of complete response (CR + CRu) as determined by an Independent Review Committee (IRC) using the International Workshop Response Criteria (IWC). Secondary measures of efficacy included IRC assessment of duration of response and objective disease response (ORR, CR + CRu + PR).

Baseline Patient Characteristics

Demographic and disease characteristics of the PTCL patients are provided in Table 5.

Table 5. Baseline Patient Characteristics (PTCL Population)

Characteristic	Study 3 (N=130)	Study 4 (N=47)
Age (years), n	130	47
Mean (SD)	59 (13)	59 (13)
Median	61	59
Sex, n (%)		
Male	88 (68)	25 (53)
Female	42 (32)	22 (47)
Race, n (%)		
White	116 (89)	40 (85)
Black	7 (5)	4 (9)
Asian	3 (2)	3 (6)
Other	4 (3)	0
PTCL Subtype Based on Central Diagnosis, n (%)		
PTCL Unspecified (NOS)	69 (53)	28 (60)
Angioimmunoblastic T-cell lymphoma (AITL)	27 (21)	7 (15)
ALK-1 negative anaplastic large cell lymphoma (ALCL)	21 (16)	5 (11)
Other	13 (10)	7 (16)
Stage of Disease, n (%)*		
I/II	39 (30)	2 (4)
III/IV	91 (70)	45 (96)
ECOG Performance Status, n (%)		
0	46 (35)	20 (43)
1	67 (51)	22 (47)
2	17 (13)	4 (9)
Number of Prior Systemic Therapies Median (Range)	2 (1, 8)	3 (1, 6)

*Stage of disease was reported at time of diagnosis for Study 3 and at time of study entry for Study 4.

All patients in both studies had received prior systemic therapy for PTCL. In Study 4, a greater percentage of patients had extensive prior radiation and chemotherapy. Twenty-one patients (16%) in Study 3 and 18 patients (38%) in Study 4 had received prior autologous stem cell transplant and 31 (24%) and 19 (40%) patients, respectively, had received prior radiation therapy.

Clinical Results

Efficacy outcomes for PTCL patients as determined by the IRC are provided in Table 6 for Study 3. The complete response rate was 15% and overall response rate was 26%. Similar complete response rates were observed by the IRC across the 3 major PTCL subtypes (NOS, AITL, and ALK-1 negative ALCL). Median time to objective response was 1.8 months (~2 cycles) for the 34 patients who achieved CR, CRu, or PR and median time to CR was 3.5 months (~4 cycles) for the 20 patients with complete response. The responses in 12 of the 20 patients achieving CR and CRu were known to exceed 11.6 months; the follow-up on the remaining 8 patients was discontinued prior to 8.5 months.

Table 6. Clinical Results for PTCL Patients

Response Rate	Study 3 (N=130)
CR+CRu, n (%)[1]	20 (15.4) [9.7, 22.8][3]
PR, n (%)[2]	14 (10.8) [6.0, 17.4][3]
ORR (CR+CRu+PR), n (%)[2]	34 (26.2) [18.8, 34.6][3]

[1] Primary Endpoint.

[2] Secondary Endpoint.

[3] Two-sided 95% Confidence Interval.

In a second single-arm clinical study in patients with PTCL who had failed prior therapy (Study 4), patients were treated with ISTODAX at a starting dose of 14 mg/m^2 infused over 4 hours on days 1, 8, and 15 every 28 days. Patients could be treated until disease progression at the discretion of the patient and the Investigator. The percentage of patients achieving CR + CRu in Study 4 was similar to that in Study 3.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

ISTODAX is supplied as a kit including a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and 22 mg of the bulking agent, povidone, USP, and hydrochloric acid, NF, as pH adjuster. In addition, each kit includes a single-dose sterile diluent vial containing 2.4 mL (2.2 mL deliverable volume) of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP.

ISTODAX® KIT containing 1 vial of romidepsin and 1 vial of diluent for romidepsin per carton.

14.2 Storage and Handling

ISTODAX (romidepsin) for injection is supplied as a kit containing 2 vials in a single carton. The carton must be stored below 25°C.

The expiry date of the product is indicated on the packaging materials

ISTODAX is a cytotoxic drug. Follow applicable special handling and disposal procedures. *[see References (15)]*.

15 MANUFACTURER:

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16 REGISTRATION HOLDER:

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17 REGISTRATION NUMBER

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