AUSTRALIAN PRODUCT INFORMATION

ISTODAX® (Romidepsin) 10mg Powder of Injection

1 NAME OF THE MEDICINE

Australian approved name: Romidepsin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 11 mg of romidepsin (inclusive of 10% overfill).

For the full list of excipients, see Section 6.1 (List of Excipients).

Description

Romidepsin is a white to off-white powder, with a melting point of 272ºC. Romidepsin is generally more soluble in organic solvents and is very slightly soluble in water (about 0.3 mg/mL). The partition coefficient (n-octanol/water) is approximately 1.9.

3 PHARMACEUTICAL FORM

Istodax is supplied in a composite pack including a sterile 10 mg single-use vial containing 10 mg of lyophilised romidepsin and 20 mg of povidone, and a second sterile vial containing 2.2 mL of solvent. The solvent vial contains 80% propylene glycol and 20% anhydrous ethanol. Both romidepsin and solvent vials contain an overfill to ensure the recommended volume can be withdrawn at a concentration of 5 mg/mL.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Istodax is indicated for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

4.2.1 Dosage

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.

4.2.2 Method of Administration

Istodax should be administered under the supervision of a physician qualified in the use of chemotherapeutic agents. Serum potassium and magnesium should be within the normal range before each administration of Istodax.

Istodax is an anti-neoplastic agent and, as with other potentially toxic compounds, caution should be exercised when preparing and handling Istodax solutions. The use of gloves is recommended.

Any unused product or waste material should be disposed of in accordance with local requirements for disposal of cytotoxic compounds.

4.2.3 Preparation and Administration

Istodax must be reconstituted with the solvent provided and further diluted with 0.9% sodium chloride injection before intravenous infusion using the following guidelines:

1. Each 10 mg single-use vial of Istodax (vial contains overfill to 11 mg of romidepsin) must be reconstituted with 2.2 mL of the supplied diluent (vial contains overfill to 2.4 mL of solvent). The final reconstituted 10 mg single-use vial contains 2.2 mL of Istodax solution 5 mg/mL.
2. With a suitable syringe, aseptically withdraw 2.2 mL of solvent from the solvent vial provided, and slowly inject it into the Istodax 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.
3. Before intravenous infusion, further dilute the reconstituted solution: Extract the appropriate amount of the reconstituted Istodax solution from the vials to deliver the desired dose. Then, using proper aseptic technique, dilute with 500 mL 0.9% Sodium Chloride Injection.
    - The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles. Parenteral drug products should be inspected visually for particulate matter and discolouration before administration, whenever solution and container permit.
    - Istodax is for single-use in one patient only, and any residue should be discarded.
    - Istodax does not contain antimicrobial preservatives. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.
4. Administer intravenously over a 4-hour period.

4.2.4 Recommended Dose Adjustments during Treatment

Haematological Toxicities

Administration of Istodax should be delayed when patients experience Grade 3 or 4 neutropenia or thrombocytopenia until the specific cytopenia returns to ANC $\geq 1.5 \times 10^9$/L and/or platelet count $\geq 75 \times 10^9$/L or baseline, then therapy may be restarted at 14 mg/m^2.

Patients who develop Grade 4 febrile (≥ 38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion should have subsequent doses of Istodax delayed until the specific cytopenia returns to Grade 1 or baseline. The Istodax dose should then be permanently reduced to 10 mg/m^2.

Non-haematologic Toxicities (except Alopecia)

Treatment with Istodax should be delayed if patients develop Grade 2 or 3 NCI CTCAE toxicity until toxicity returns to Grade 1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs or Grade 4 toxicity is observed, 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.

Istodax should be permanently discontinued for NCI CTCAE Grade 3 or 4 toxicity that is recurrent despite dose reduction.

Use in Patients with Hepatic Impairment

Dose adjustment is not required for patients with mild hepatic impairment. Dose adjustment is recommended in patients with moderate and severe hepatic impairment.

For patients with moderate hepatic impairment, a dose adjustment of 7 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle (50% dose reduction) is recommended. Cycles are to be repeated every 28 days provided that the patient continues to tolerate treatment with Istodax and continues to benefit from treatment. (See Table 1).

For patients with severe hepatic impairment, a dose adjustment of 5 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle (64% dose reduction) is recommended. Cycles are to be repeated every 28 days provided that the patient continues to tolerate treatment with Istodax and continues to benefit from treatment. (See Table 1).

Table 1 below lists the recommendations for dose adjustment in Patient with Hepatic Impairment.

Table 1: Recommendations for Dose Adjustment in Patients with Hepatic Impairment

	Bilirubin Levels	**AST Levels**	**Istodax Dose**
Mild	<ULN	AST > ULN	14 mg/m^2
	>ULN but ≤ 1.5 x ULN	any AST	
Moderate	> 1.5 x ULN to ≤ 3 x ULN	any AST	7 mg/m^2
Severe	> 3 x ULN	any AST	5 mg/m^2

Use in Patients with Renal Impairment

No formal studies have been conducted in patients with renal impairment. Patients with serum creatinine > 176.8 µmol/L were excluded from the pivotal study. However, renal excretion does not play a significant role in the elimination of romidepsin as metabolism is primarily hepatic. A population PK analysis showed that romidepsin PK were not affected by different levels of renal impairment. However, as the effect of end-stage renal disease has not been studied, patients with end-stage renal disease should be treated with caution.

4.3 CONTRAINDICATIONS

Hypersensitivity to romidepsin or any of the excipients.

4.4 . SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1 Haematological Toxicity

Treatment with Istodax can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia) and anaemia; therefore, these haematological parameters should be monitored during treatment with Istodax, and the dose should be modified as necessary.

4.4.2 Infection

Serious and sometimes fatal infections, including pneumonia, sepsis, and viral reactivation (including hepatitis B and Epstein Barr viruses) have been reported in clinical trials with Istodax. These can occur during treatment and within 30 days after treatment, and the risk of life-threatening infections 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.

Reactivation of hepatitis B virus infection has occurred in 1% of PTCL patients in clinical trials in Western populations. Consider monitoring or prophylaxis in patients with evidence of a past history of hepatitis B.

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.

4.4.3 Electrocardiographic Changes

QTc prolongation as well as several treatment-emergent morphological changes in ECGs (including Twave 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 treatmentemergent 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.

Appropriate cardiovascular monitoring precautions should be considered in patients with congenital long QT syndrome, a history of significant cardiovascular disease, and those taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation. Such precautions include the monitoring of ECGs at baseline and periodically during treatment.

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.

4.4.4 Gastrointestinal Disturbances

Nausea and vomiting have very commonly been reported with Istodax; therefore, anti-emetic use is recommended.

4.4.5 Tumour Lysis Syndrome

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

4.4.6 Hypersensitivity

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

4.4.7 Use in the elderly

No specific dose adjustments are recommended for the elderly. The population PK analysis of romidepsin showed that age did not appear to influence the romidepsin PK.

4.4.8 Paediatric use

The safety and efficacy of romidepsin in children and adolescents under 18 years of age has not been established.

4.4.9 Effects on laboratory tests

See sections 4.4.1 Haematological toxicity and 4.4.3 Electrocardiographic Changes.

4.5 . INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

4.5.1 Warfarin or Warfarin Derivatives

Prolongation of prothrombin time (PT) and elevation of International Normalisation Ratio (INR) were observed in a patient receiving Istodax concomitantly with warfarin. Although the interaction potential between Istodax and warfarin or warfarin derivatives has not been formally studied, physicians should carefully monitor PT and INR in patients concurrently administered Istodax and warfarin or warfarin derivatives.

4.5.2 Medicines that Prolong the QT Interval

Appropriate cardiovascular monitoring precautions should be considered in patients taking antiarrhythmic medicines or medicinal products that lead to significant QT prolongation. Such precautions include the monitoring of ECGs at baseline and periodically during treatment.

4.5.3 Medicines that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Romidepsin is metabolized by CYP3A4. Strong CYP3A4 inhibitors increase concentrations of romidepsin. In a pharmacokinetic medicine interaction trial, the strong CYP3A4 inhibitor, ketoconazole, increased romidepsin exposure ($AUC_{0-\infty}$) by approximately 25%. Monitor for toxicity related to increased romidepsin exposure when romidepsin is co-administered with strong CYP3A4 inhibitors.

Avoid co-administration of Istodax with rifampin. In a pharmacokinetic medicine interaction trial with co-administered rifampin (a strong CYP3A4 inducer), romidepsin exposure was increased by approximately 80% and 60% for $AUC_{0-\infty}$ and C_{max} respectively. Typically, co-administration of CYP3A4 inducers decreases concentrations of medicines metabolised by CYP3A4. The reasons for this increase are not understood. It is unknown if other potent CYP3A4 inducers would alter the exposure of Istodax. Therefore, the use of other potent CYP3A4 inducers should be avoided when possible.

4.5.4 Medicines that Inhibit Medicine Transport Systems

Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). Although romidepsin is a substrate, P-gp inhibitors are not likely to affect pharmacokinetics of romidespin as it is extensively metabolized before elimination.

4.5.5 Oestrogen-Containing Contraceptives

An *in vitro* binding assay determined that romidepsin competes with beta-oestradiol for binding to oestrogen receptors. Women of childbearing potential should be advised that Istodax may reduce the effectiveness of oestrogen-containing contraceptives. Therefore, alternate methods of non-oestrogencontaining contraception (e.g., condoms, intrauterine device) should be used in patients receiving romidepsin. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.

4.6 . FERTILITY, PREGNANCY AND LACTATION

4.6.1 Effects on fertility

Formal studies to assess the effect of romidepsin on fertility have not been conducted.

Based on non-clinical 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/week (approximately 2% of the exposure level in patients receiving the recommended dose of 14 mg/m^2/dose). Atrophy was seen in the ovary, uterus, vagina and mammary gland of female rats administered doses at ≥ 0.1 mg/kg/week (approximately 0.3% of the exposure level in patients receiving the recommended dose of 14 mg/m^2/dose).
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, approximately 2% of the estimated human weekly dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were also observed.

Testicular degeneration was observed in dogs and mice, and atrophy of the prostate was also seen in dogs following administration of romidepsin at exposures below the clinical AUC.

4.6.2 Use in pregnancy (Category D)

There are no adequate and well-controlled studies of Istodax in pregnant women. Women of childbearing potential should have a pregnancy test prior to starting treatment with Istodax. Based on its mechanism of action and findings in animals, Istodax can cause foetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Istodax. Women of childbearing potential should be advised to use effective contraception during treatment with Istodax and for at least 1 month after the last dose. Istodax may reduce the effectiveness of oestrogen-containing contraceptives. Therefore, alternative methods of non-oestrogen containing contraception (e.g. condoms, intrauterine device) should be used in patients receiving Istodax.

Male patients treated with Istodax are advised to use effective contraception and to avoid fathering a child during and up to 1 month after treatment.

4.6.3 Use in Lactation

There is no information regarding the presence of romidepsin in human milk, the effects of Istodax on the nursing infant, or the effects of Istodax on milk production. A risk to the newborn or infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from Istodax therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

4.7 . EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects of Istodax on the ability to drive or operate machines have been performed. Treatment with romidepsin in clinical trials was commonly associated with asthenia and fatigue, which can be severe. If affected, patients are to be instructed not to drive or use machines or perform hazardous tasks.

4.8 . ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

4.8.1 Tabulated Summary of Adverse Events

In a single-arm study, 131 patients with PTCL were exposed to romidepsin at a dose of 14 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle. The mean duration of treatment and number of doses were 5.6 months and 15.5 doses, respectively, corresponding to about 6 cycles.

Table 2 below lists the adverse events that occurred at a frequency of ≥ 10% and adverse drug reactions (considered related to the treatment) that occurred at a frequency of ≥ 5% in subjects. The table also provides the respective ≥ Grade 3 events under each section.

Table 2. Most Frequently Reported Adverse Events and Adverse Drug Reactions in Study GPI-060002 (as treated population, N=131)

System organ class **Preferred term**	**All Adverse Events**		**Adverse Drug Reactions (related events)**	
	All Grades (Cut-off ≥ 10%) n (%)	**≥ Grade 3 n (%)**	**All Grades (Cut-off ≥ 5%) n (%)**	**≥ Grade 3 n (%)**
Any adverse events	*128 (97)*	*88 (67)*	*121 (92)*	*68(52)*
Gastrointestinal Disorders				
Nausea	77 (59)	3 (2)	71 (54)	2 (2)
Vomiting	51 (39)	6 (5)	44 (34)	5 (4)
Diarrhoea	47 (36)	3 (2)	30 (23)	2 (2)
Constipation	39 (30)	1 (< 1)	19 (15)	0
Abdominal pain	18 (14)	3 (2)	8 (6)	0
Stomatitis	14 (11)	0	9 (7)	0
Dyspepsia	-	-	6 (5)	0

General Disorders and Administration Site Conditions				
Asthenia/Fatigue*	72 (55)	11 (8)	68 (52)	7 (5)
Pyrexia	46 (35)	8 (6)	23 (18)	6 (5)
Chills	14 (11)	1 (< 1)	6 (5)	0
Oedema peripheral	13 (10)	1 (< 1)	-	-
Blood and Lymphatic System Disorders				
Thrombocytopenia	53 (41)	32 (24)	52 (40)	30 (23)
Neutropenia	39 (30)	26 (20)	38 (29)	24 (18)
Anaemia	33 (25)	14 (11)	28 (21)	7 (5)
Leukopenia	16 (12)	8 (6)	16 (12)	8 (6)
System organ class **Preferred term**	**All Adverse Events**		**Adverse Drug Reactions (related events)**	
	All Grades (Cut-off ≥ 10%) n (%)	**≥ Grade 3 n (%)**	**All Grades (Cut-off ≥ 5%) n (%)**	**≥ Grade 3 n (%)**
Metabolism and Nutrition Disorders				
Anorexia	37 (28)	2 (2)	34 (26)	2 (2)
Decreased appetite	-	-	12 (9)	1 (1)
Hypokalaemia	14 (11)	3 (2)	7 (5)	2 (2)
Hypomagnesaemia	-	-	7 (5)	0
Nervous System Disorders				
Dysgeusia	27 (21)	0	27 (21)	0
Headache	19 (15)	0	14 (11)	0
Dizziness	-	-	7 (5)	0
Lethargy	-	-	6 (5)	0
Musculoskeletal and Nutrition Disorders				
Muscle spasms	-	-	9 (7)	0
Myalgia	-	-	7 (5)	1 (1)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	23 (18)	0	-	-
Dyspnoea	17 (13)	3 (2)	7 (5)	1 (1)
Skin and Subcutaneous Tissue Disorders				

Rash	-	-	7 (5)	0
Investigations				
Weight decreased	14 (11)	0	10 (8)	0
Cardiac Disorders				
Tachycardia	13 (10)	0	6 (5)	0
Infections				
Upper respiratory tract infections	-	-	6 (5)	2 (2)
Vascular Disorders				
Hypotension	-	-	6 (5)	1 (1)

*Combined MedDRA terms are presented instead of individual terms to provide a more accurate representation of similar types of adverse drug reactions.
The symbol (-) indicates that the term does not meet the relevant cut-off for inclusion in that column.

4.8.2 Summary of Adverse Reactions

The principal clinically important groups of adverse drug reactions in patients with PTCL treated with romidepsin are gastrointestinal disturbances, asthenic conditions, infections, haematological toxicities and clinical chemistry abnormalities.

Gastrointestinal Disturbances

Gastrointestinal (GI) reactions, such as nausea, vomiting and diarrhoea were commonly reported but generally mild to moderate in intensity and non-serious, and most patients continued romidepsin despite the occurrence of GI events. In accordance with the study protocols, anti-emetic support was commonly used. Dehydration concurrent with vomiting and/or diarrhoea was uncommon.

Asthenic Conditions

Asthenic conditions generally presented early during treatment and were mostly Grade 1 or 2 in intensity and non-serious. However, Grade 3 or 4 and/or serious asthenic conditions have been reported. Asthenic conditions were an infrequently reported cause of discontinuation in patients with PTCL (< 2%).

Haematological Toxicities and Clinical Chemistry

The incidence of haematologic toxicities including neutropenia and thrombocytopenia was common in patients with PTCL and were more often Grade 3 or 4. Both thrombocytopenia and neutropenia commonly led to a dose being held, or less commonly to dose reduction or discontinuation in a few patients. Hypokalaemia was also commonly observed in PTCL.

In a separate phase 2, multicenter, open-label study designed to evaluate the activity and tolerability of romidepsin in patients with PTCL who had received prior systemic therapy conducted by the National Cancer Institute (NCI) - Study 1312, a higher incidence of adverse drug reactions related to clinical chemistry abnormalities were noted compared to the pivotal trial, due to more intensive monitoring and routine reporting of laboratory abnormalities as adverse events without consideration of their clinical significance. These include the following (frequency provided for the NCI study versus that in the pivotal trial): hypocalcaemia (47% vs. 2%), increased aspartate transaminase (34% vs. 3%), increased alanine

transaminase (32% vs. 3%), hypoalbuminemia (32% vs. 0%), hypomagnesaemia (26% vs. 5%), hyperglycaemia (17% vs. 1%), and hypokalaemia (15% vs. 5%). Most patients continued treatment unchanged despite the occurrence of these reactions, and only two patients were required to permanently discontinue therapy due to these reactions.

Infections

In patients with PTCL, infections were commonly observed (57%), and the most commonly reported types were upper respiratory tract infection (9%), pneumonia and urinary tract infection (7%), oral candidiasis (6%), and sepsis and nasopharyngitis (5%).

Tumour Lysis Syndrome

Tumour lysis syndrome (tls) has been reported to occur in patients with advanced disease and 2% of patients with stage III/IV PTCL.

Discontinuations

Discontinuation due to an adverse event occurred in 19% of patients in the study. Thrombocytopenia and pneumonia were the only events leading to treatment discontinuation in at least 2% of patients.

Serious Adverse Events

Infections were the most common type of serious adverse events (SAEs) reported, with 20% of patients experiencing a serious infection during the study. SAEs reported in ≥ 2% of patients in the study were pyrexia (8%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnoea, and dehydration (2%).
Reactivation of hepatitis B virus infection has occurred in 1% of PTCL patients in clinical trials in Western populations. Consider monitoring or prophylaxis in patients with evidence of a past history of hepatitis B.

Deaths

In the clinical trial, 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.

4.8.3 Post-marketing data

Viral reactivation (hepatitis B and Epstein Barr viruses) was reported from clinical trials in the postmarketing setting.

4.8.4 Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Expected manifestations of overdose could include GI disturbances (nausea, vomiting, diarrhoea, and constipation), haematologic toxicity (thrombocytopenia, neutropenia, and anaemia), asthenic conditions

(e.g., fatigue, asthenia, and lethargy), infections, and ECG changes. No specific information is available on the treatment of overdosage of Istodax. There is no known antidote for romidepsin and it is not known if romidepsin is dialyzable.

In the event of an overdose, close clinical monitoring may be instituted and supportive therapy given as required. For information on the management of overdose, in Australia, contact the Poisons Advisory Centre on 13 11 26. In New Zealand. Contact the National Poisons Centre on 0800 POISON or 0800 764 766 for advise on management.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Cytostatic anti-cancer therapy.

5.1.1. Mechanism of Action

Romidepsin is an anti-neoplastic agent that belongs to the class of drugs known as histone deacetylase (HDAC) inhibitors. At nanomolar concentrations, romidepsin exhibited anti-cancer activity against both haematological and solid tumour lines. Romidepsin has been shown to have pleiotropic activity including HDAC inhibition, induction or repression of gene expression, cell cycle arrest, cell differentiation, cell growth inhibition, and induction of apoptosis. Romidepsin exposure has been shown to cause both the induction and repression of a number of key regulatory genes *in vitro* and *in vivo*.

5.1.2 Cardiac Electrophysiology

The potential effect of romidepsin on the QTc/QTcF interval (heart rate corrected) was evaluated in 26 subjects 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. No concentration-dependent effect of romidepsin on the duration of the QTc interval was identified at maximum plasma concentrations (C_{max}) up to 2.5-fold higher on average than observed with the clinical dose regimen of 14 mg/m^2 administered as a 4-hour infusion. Central tendency and categorical analyses also showed no effect of romidepsin on the duration of the QTc/QTcF interval. Based on these results, romidepsin does not appear to prolong the QTc interval to a clinically significant extent in patients with advanced cancer.

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 (bpm) occurring at the 6-hour time point 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 4.7 bpm.

5.1.3 Clinical trials

Istodax was evaluated in a multicenter, single-arm, international clinical study in patients with peripheral T-cell lymphoma (PTCL) who had failed at least 1 prior systemic therapy (Study GPI-06-0002). Patients in the USA, 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 of 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 the complete response (CR) rate (comprising CR and unconfirmed CR [CRu]) along with duration of response, as determined by an Independent Review Committee (IRC). The IRC were blinded to investigator evaluations, and conducted a prospective 2-step assessment including review of radiological data and relevant clinical and pathological data using the International Workshop Criteria (IWC).

Supportive measures of efficacy included IRC assessment of objective disease response (comprising objective response rate [ORR], CR, CRu and partial response [PR]) and Investigator assessments of CR, objective disease response and duration of response. Additional secondary endpoints included time to objective disease progression and change in ECOG performance status.

Most patients (91 [70%]) had Stage III or IV disease at the time of initial PTCL diagnosis. All patients had received prior systemic therapy for PTCL. Twenty-one patients (16.2%) had received prior autologous stem cell transplant.

Efficacy outcomes for the HC population (n = 130) as determined by the IRC and Investigators are provided in **Table 3**. The CR rate was 15% and ORR was 26% as determined by the IRC. Stable disease was reported as best response in 25% of patients. Similar CR rates were observed by the IRC across all major subtypes of PTCL: PTCL NOS (14.5%); AITL (22.2%); and ALK-1 negative ALCL (19.0%).

Among the 49 patients whose best response to last prior therapy was progressive disease, 9 (18.4%) achieved CR (8 of these 9 patients achieved a complete response with durations of response ≥ 6 months, including 4 patients with durations ≥ 12 months) and 14 (28.6%) achieved objective disease response.

Responses to romidepsin generally occurred early in the course of therapy. Median time to objective response was 1.8 months ([observed at ~ 2 cycles] [range - 1.4 to 5.3 months]) for the 34 patients who achieved CR, CRu or PR, and the median time to CR was 3.5 months ([observed at~ 4 cycles] [range - 1.6 to 9.2 months]) for patients with CR, based on IRC review. There are insufficient data from the pivotal study to support guidance on the potential benefit of haematopoietic stem cell transplantation in patients achieving a complete response with romidepsin.

Table 3. Response Rates Based on Overall IRC and Investigators' Assessments (HC Population)

Endpoint	**IRC (N=130)**	**Investigators (N=130)**
Response Rate		
ORR (CR+CRu+PR), n (%)	34 (26.2) [18.8, 34.6][1]	38 (29.2) [21.6, 37.8][1]
CR+CRu, n (%)	20 (15.4) [9.7, 22.8][1]	21 (16.2) [10.3, 23.6][1]
PR, n (%)	14 (10.8)	17 (13.1)
SD, n (%)	32 (24.6)	22 (16.9)
Duration of Response (months)		
ORR		

N	34 [< 1, 56*]	38 [< 1, 56*]
Median (range)	NE [12, NE][1]	12 [8, NE][1]
CR + CRu		
N	20 [< 1, 56*]	21 [1, 56*]
Median (range)	NE [16, NE][1]	NE [12, NE][1]

CR = Complete response; CRu = Complete response (unconfirmed); IRC = Independent Review Committee; ORR = Objective response rate; PR = Partial response; SD = Stable disease.

*denotes censored value; NE = Not Estimated

1. Two-sided 95% Confidence Interval;

5.2 PHARMACOKINETIC PROPERTIES

5.2.1 Absorption

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

Following the start of a 4-hour infusion at 14 mg/m² in patients with advanced malignancies, romidepsin plasma concentrations increased rapidly and reached a plateau (~ 90% of C_{max}) at approximately 1-hour post infusion initiation. After the end of the infusion (i.e., 4-hour), concentrations declined in an apparent multiphasic manner. Based on the non-compartmental analysis, romidepsin $AUC_{0-\infty}$ [geometric mean (geometric CV%)] was 3,157 ng*hr/mL (33.9%) with a mean peak plasma concentration (C_{max}) of 761 ng/mL (31.2%).

5.2.2 Distribution

Romidepsin is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1000 ng/mL with alpha-1-acid-glycoprotein (AAG) being the principal binding protein.

Romidepsin is not a substrate for BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 transporters. At therapeutically relevant concentrations, romidepsin did not cause a notable inhibition of BCRP, MDR1, BSEP, MRP2, OAT1, OAT3, OATP1B3, or OCT2. Therefore, romidepsin is not anticipated to cause or be subject to clinically relevant interactions when coadministered with substrates or inhibitors of these transporters. Romidepsin caused modest inhibition of OATP1B1 (36-80% at 110 µM). Clinical drug-drug interactions with OATP1B1 substrates cannot be excluded.

5.2.3 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 CYP P450 induction or inhibition by romidepsin when co-administered with CYP P450 substrates.

5.2.4 Excretion

Based on the non-compartmental analysis following 4-hour intravenous administration of romidepsin at 14 mg/m^2, romidepsin clearance [geometric mean (geometric CV%)] was 8.4 L/hr (36.8) and terminal elimination half-life was 3.7 hr (8.3%).

5.2.6 Effect of Hepatic Impairment

In patients with cancer, the pharmacokinetics of romidepsin in 12 patients with normal hepatic function (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ ULN), 8 patients with mild hepatic dysfunction (B1: bilirubin ≤ULN and AST > ULN; B2: bilirubin > ULN but ≤ 1.5 x ULN and any AST), 5 patients with moderate hepatic dysfunction (bilirubin > 1.5 x ULN to ≤ 3 x ULN and any AST), and 6 patients with severe hepatic dysfunction (bilirubin > 3 x ULN and any AST) were compared following a single 4-hour intravenous infusion dose administration of romidepsin at 14 mg/m^2, 14 mg/m^2, 7 mg/m^2, and 5 mg/m^2, respectively. The geometric mean C_{max} values after administration of 14, 7, and 5mg/m^2 romidepsin in patients with mild, moderate, and severe hepatic impairment 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. For the 4 cohorts, moderate inter-patient variability was noted for the exposure parameters, as coefficient of variation (CV) ranged from 29 to 56%. Consistent with the overall exposure (AUC_{inf}) results, compared to the normal hepatic function cohort, romidepsin clearance decreased with increase hepatic impaired function.

The ranges of individual C_{max} and AUC_{inf} values observed from mild, moderate and severe hepatic impaired patients are similar to the range observed from the normal hepatic function patients. This suggests that for patients with mild, moderate, and severe impaired hepatic function, a dose of 14, 7, and 5 mg/m^2, respectively, provide similar exposure as compared to patients with normal hepatic function. Therefore, for patients with mild, moderate, and severe hepatic dysfunction, it is recommended to use a starting romidepsin dose of 14 mg/m^2, 7 mg/m^2, and 5mg/m^2, respectively, administered as a 4-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle.

5.2.6 Medicine Interactions

Ketoconazole: A medicine interaction clinical trial with the strong CYP3A4 inhibitor, ketoconazole, was conducted in patients with advanced cancer. 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 $AUC_{0-\infty}$ was statistically significant. Coadministration of ketoconazole slightly decreased the romidepsin clearance and volume of distribution, but did not have a statistically significant effect on peak exposure (C_{max}).

Rifampin: A medicine interaction clinical trial with the strong CYP3A4 inducer, rifampin, was conducted in patients with advanced cancer. 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 two treatments was statistically significant. Co-administration of rifampin decreased the romidepsin clearance and volume of distribution by 44% and 52%, respectively. The reasons for this increase are not understood.

5.3 PRECLINICAL SAFETY DATA

5.3.1 Genotoxicity

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.

5.3.2 Carcinogenicity

Carcinogenicity studies have not been performed with romidepsin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Istodax contains Povidone 22 mg per vial (inclusive of 10% overfill used).

Solvent

2.4 mL (inclusive of overfill to ensure 2.2 mL deliverable volume) of a solution comprising 80% propylene glycol and 20% anhydrous ethanol.

6.2 INCOMPATIBILITIES

Incompatibilities were not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Unopened vial of Istodax (romidepsin) for injection: 36 months
Unopened vial of Diluent for Istodax: 36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store unopened vials of Istodax and solvent below 25°C. Store vials in carton until use.

6.5 NATURE AND CONTENTS OF CONTAINER

Istodax is supplied as a composite pack with a sterile 10 mg single-use vial containing 10 mg of lyophilised romidepsin (vial contains an overfill to 11 mg of romidepsin), and a second sterile vial containing 2.2 mL of diluent (vial contains an overfill to 2.4 mL of solvent).

Istodax 10 mg powder vial: 10 mL glass vial (type I) with a 20 mm butyl rubber stopper.

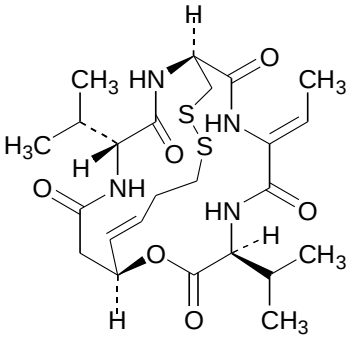
Solvent: 2 mL glass vial (type I) with a 13 mm butyl Teflon-faced plug stopper.

Istodax composite pack containing 1 vial of romidepsin and 1 vial of solvent.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements for disposal of cytotoxic compounds.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure	
CAS number	128517-07-7
Molecular formula:	$C_{24}H_{36}N_4O_6S_2$
Molecular weight:	540.71
ATC code:	L01XX39
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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL

07 August 2013

10 DATE OF REVISION

22 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Update the sponsor's details.