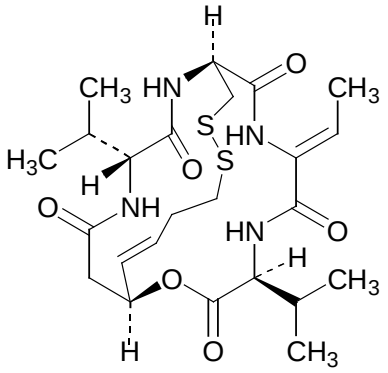
Attachment 1: Product information for AusPAR Istodax; romidepsin; Celgene Australia Pty Ltd; PM-2012-01446-3-4 Date of Finalisation 20 November 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

ISTODAX® (romidepsin) Powder for Injection

i) Name of the medicine

Australian approved name:	Romidepsin
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.
Chemical Abstract Service (CAS) registry number:	128517-07-7
Chemical structure:	



ii) 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 co-efficient (n-octanol/water) is approximately 1.9.

Istodax is supplied in a composite pack including: a sterile single-use vial containing 10 mg of lyophilised romidepsin and 20 mg povidone, and a second sterile vial containing 2 mL of solvent. The solvent vial contains 80% propylene glycol and 20% anhydrous ethanol.

iii) Pharmacology

Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatic anti-cancer therapy.

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*.

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 bpm occurring at the 6-hour time point for patients receiving 14 mg/m^2 as a 4-hour infusion. At 24 hours, the mean increase in heart rate was 4.7 bpm.

Pharmacokinetic properties

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.

In the noncompartmental analysis of initial dose PK data from 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, the geometric mean value of the C_{max} was 377 ng/mL and the area under the plasma concentration versus time curve ($AUC_{0-\infty}$) was 1549 ng*hr/mL.

Distribution

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

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.

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 romidepsin was observed after repeated dosing.

Pharmacokinetics in the Elderly

The population PK analysis showed that age did not appear to influence romidepsin PK.

iv) 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. 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 1. The CR rate was 15% and ORR was 25% 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 (18.5%); 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 (range, 1.4 to 5.3 months, observed at ~ 2 cycles) for the 33 patients who achieved CR, CRu or PR based on IRC review and the time to CR was 3.7 months (range, 1.6 to 13.7 months, observed at~ 4 cycles) for patients with CR. 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 1: Response Rates Based on Overall IRC and Investigators' Assessments (HC Population)

	IRC (N=130)	**Investigators (N=130)**
Response Rate		
ORR (CR+CRu+PR), n (%)	33 (25.4) [18.2][1]	38 (29.2) [21.6][1]
CR+CRu, n (%)	19 (14.6) [9.0][1]	21 (16.2) [10.3][1]
PR, n (%) (SD) n (%)	14 (10.8) 33 (25.4)	17 (13.1) 22 (16.9)
Duration of Response (months)		
ORR		

N	33	38
Median (range)	17 (< 1, 35*)	12 (< 1, 35*)
CR + CRu		
N	19	21
Median (range)	17 (< 1, 35*)	NE (1, 35*)

1 Lower bound of 95% Confidence Interval; *denotes censored value; NE = Not Estimatable

v) Indication

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

vi) Contraindications

Hypersensitivity to romidepsin or any of the excipients.

vii) Precautions

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.

2. Use in Pregnancy (Category D)

There are no adequate and well-controlled studies of Istodax in pregnant women. However, based on its mechanism of action, Istodax may cause foetal harm when administered to a pregnant woman. In rats, romidepsin was embryocidal and teratogenic to the developing foetus at exposures below those in patients at the recommended dose.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Istodax. If Istodax is used during pregnancy, or if the patient becomes pregnant while taking Istodax, the patient should be advised of the potential harm to the foetus.

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.

In rats intravenously administered romidepsin at IV doses of 0.1, 0.2 or 0.5 mg/kg/day during the period of organogenesis, complete resorption or post-implantation loss was observed at 0.5 mg/kg/day, associated with maternal toxicity. Rotated hindlimbs, folded retina and delayed skeletal ossification were observed at ≥ 0.2 mg/kg/day and decreased foetal weights at all doses. The systemic exposures (AUC) in pregnant rats were 1-8% of the human exposure at the recommended clinical dose of 14 mg/m^2/week.

3. 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 (see section x. [Dosage and Administration]).

4. Infection

Serious and sometimes fatal infections, including pneumonia and sepsis, have been reported in clinical trials with Istodax. These can occur during treatment and within 30 days after treatment.

5. Electrocardiographic Changes

QTc prolongation as well as several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. Many of the ECG morphologic abnormalities were also observed at baseline. These ECG changes were transient and were not associated with functional cardiovascular changes or with symptoms. The clinical significance of these treatment-emergent 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 (see "Cardiac Electrophysiology" in section iii. [Pharmacology]). 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.

6. Gastrointestinal Disturbances

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

7. 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.

8. Hypersensitivity

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

9. Use in Lactation

It is not known whether romidepsin is excreted in human milk. Because many medicines are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

10. Paediatric Use

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

11. 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.

12. 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.

13. Carcinogenicity

Carcinogenicity studies have not been performed with romidepsin.

viii) Interaction with other Medicines

No formal clinical medicine interaction studies with Istodax have been conducted.

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.

Medicines that Prolong the QT Interval

Appropriate cardiovascular monitoring precautions should be considered in patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation (see "Cardiac Electrophysiology" in section iii. [Pharmacology]), and "Electrocardiographic Changes" in section vii. Precautions). Such precautions include the monitoring of ECGs at baseline and periodically during treatment.

Medicines that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Romidepsin is metabolized by CYP3A4. Although there are no formal medicine interaction studies for Istodax, strong CYP3A4 inhibitors may increase concentrations of romidepsin. Therefore, co-administration with strong CYP3A4 inhibitors should be avoided if possible. Caution should also be exercised with concomitant use of moderate CYP3A4 inhibitors. Co-administration of potent CYP3A4 inducers may decrease concentrations of romidepsin and should be avoided if possible. Patients should also refrain from taking St. John's Wort.

Medicines that Inhibit Medicine Transport Systems

Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If Istodax is administered with medicines that inhibit P-gp, increased concentrations of romidepsin are likely, and caution should be exercised.

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-oestrogen-containing contraception (e.g., condoms, intrauterine device) should be used in patients receiving romidepsin (see section vii. [Precautions]). Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.

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 (see section ix. [Adverse Effects]). If affected, patients are to be instructed not to drive or use machines to perform hazardous tasks.

ix) Adverse Effects

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 3.5 months and 11 doses, respectively, corresponding to about 4 cycles.

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

Table 2 - Most Frequently Reported Adverse Events and Adverse Reactions in Study GPI-06-0002) (as treated population, N=131)

	All adverse events		**Adverse drug reactions (related events)**	
System organ class **Preferred term**	**All Grades (Cut-off ≥ 10%) n (%)**	**≥ Grade 3 n (%)**	**All Grades (Cut-off ≥ 5%) n (%)**	**≥ Grade 3 n (%)**
Any adverse events	*127 (97)*	*86 (66)*	*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	13 (10)	0	9 (7)	0
Dyspepsia	-	-	6 (5)	0
General disorders and administration site conditions				
Asthenia/Fatigue*	72 (55)	11 (8)	68 (51.9)	7 (5)
Pyrexia	46 (35)	7 (5)	22 (17)	5 (4)
Chills	14 (11)	1 (< 1)	6 (5)	0
Oedema peripheral	13 (10)	1 (< 1)	-	-

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 (%)
Blood and lymphatic system disorders				
Thrombocytopenia	53 (41)	32 (24)	52 (40)	30 (23)
Neutropenia	39 (30)	26 (20)	38 (29)	24 (18)
Anaemia	32 (24)	14 (11)	27 (21)	7 (5)
Leukopenia	16 (12)	8 (6)	16 (12)	8 (6)
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	-	-	8 (6)	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	13 (10)	0	10 (8)	0
Cardiac disorders				
Tachycardia	13 (10)	0	6 (5)	0
Infections				
Upper respiratory tract infections	-	-	6 (5)	0
Vascular disorders				
Hypotension	-	-	6 (5)	1 (1)

*Combined MedDRA terms are reported 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.

The principal clinically important groups of adverse 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 (55%), and the most commonly reported types were upper respiratory tract infection (8%), urinary tract infection (7%), pneumonia (6%), and sepsis and oral candidiasis (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 (SAE) reported, with 19% of patients experiencing a serious infection during the study. SAEs reported in ≥ 2% of patients in the study were pyrexia (7%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnoea, and dehydration (2%).

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.

Post marketing data

No additional safety signals have been observed from post-marketing experience.

x) Dosage and 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.

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 must be reconstituted with 2 mL of the supplied solvent: With a suitable syringe, aseptically withdraw 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 should contain Istodax 5 mg/mL.

2. 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.

3. Administer intravenously over a 4-hour period.

Recommended 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.

Dosage 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 x 10^9/L and/or platelet count $\geq$ 75 x 10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.

Patients who develop Grade 4 febrile ($\geq$ 38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion should have subsequent doses of Istodax delayed until 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/dose. 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/dose.

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

No formal studies have been conducted in patients with hepatic impairment. Patients with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin > 2x upper limit of normal (ULN) (> 3x ULN in the presence of liver metastases) were excluded from the pivotal clinical study. A population PK analysis showed that mild hepatic impairment [total bilirubin (TB) ≤ ULN and AST > ULN; or TB > 1.0x - 1.5x ULN and any AST] had no significant influence on romidepsin PK. The effect of moderate (TB > 1.5x - 3x ULN and any AST) and severe (TB > 3x ULN and any AST) hepatic impairment on romidepsin PK is unknown. Because romidepsin is primarily eliminated through metabolism, patients with moderate and severe hepatic impairment should be treated with caution.

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.

xi) Overdosage

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.

xii) Presentation and Storage Conditions

Presentation

Istodax is supplied as a composite pack with a sterile single-use vial containing 10 mg of lyophilised romidepsin, and a second sterile vial containing 2 mL of solvent.

Romidepsin is a white to off-white lyophilised sterile powder for concentrate for solution for infusion. The solvent is a clear colourless solution.

Composition:

Active:

Romidepsin 10 mg per vial.

Excipients:

Povidone 20 mg per vial

Solvent:

2 mL of a solution comprising 80% propylene glycol and 20% anhydrous ethanol.

Storage conditions

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

Container type

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 10 mg and 1 vial of solvent 2 mL.

xiii) Name and Address of the sponsor

Sponsored in Australia by:

Celgene Pty Limited
Level 7, 607 St Kilda Road,
Melbourne, Victoria 3004.
Australia.

xiv) Poison Schedule of the medicine

Schedule 4 (Prescription Only Medicine)

xv) Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

07 August 2013