



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Romidepsin

Proprietary Product Name: Istodax

Sponsor: Celgene Pty Ltd

November 2013

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	30 July 2013
<i>Active ingredient:</i>	Romidepsin
<i>Product name:</i>	Istodax
<i>Sponsor's name and address:</i>	Celgene Australia Pty Ltd Level 7, 607 St Kilda Road Melbourne VIC 3004
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	10 mg/2 mL
<i>Container:</i>	Glass vial
<i>Pack size:</i>	Carton with 1 powder for injection vial and 1 solvent vial
<i>Approved therapeutic use:</i>	Istodax is indicated for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage (abbreviated):</i>	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.
<i>ARTG number:</i>	198854

Product background

Romidepsin is an inhibitor of histone deacetylase (HDAC) and other proteins that regulate cell function including gene expression, cell proliferation, migration and apoptosis.

This AusPAR describes the application by Celgene Australia Pty Ltd (the sponsor) to register romidepsin powder for intravenous (IV) infusion for the following indication:

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

Romidepsin (Istodax) 10 mg powder for injection received Orphan Drug designation by the TGA on 27 August 2010 for the treatment of patients with:

- peripheral T-cell lymphoma (PTCL) who have received at least one prior systemic therapy; and
- cutaneous T-cell lymphoma (CTCL) who have received at least one prior systemic therapy.

Peripheral T-cell lymphoma is a subtype of Non-Hodgkin's lymphoma affecting T-cells outside the thymus. Without treatment, prognosis is often poor and there is a high relapse rate. There is currently no clear consensus on how to manage this condition.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 7th August 2013.

At the time this application was considered by the TGA a similar application was approved in the US (for CTCL in 2009 and for PTCL in 2011) and was under review in Canada, Switzerland, Israel and South Korea.

The sponsor advised that an application for the use of romidepsin in PTCL received a negative decision in the European Union (EU) for the following reason: *The CHMP's main concern was that it could not conclude on the clinical benefit-risk ratio of Istodax due to the absence of a comparator in the pivotal Phase II study (GPI-06-002).*

Product Information

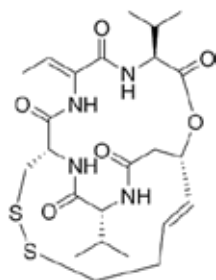
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Romidepsin is a disulfide-bridged, bicyclic depsipeptide¹ with molecular formula C₂₄H₃₆N₄O₆S₂ and molecular weight 540.71 g/mol. Its structure is shown in Figure 1. Romidepsin is produced by fermentation using a strain of the soil bacterium *Chromobacterium (C.) violaceum*. *C. violaceum* is a coccobacillus found in water and soil in tropical and subtropical regions, including Australia, which can rarely cause human disease. Istodax cannot cause infection.

¹ A peptide in which one or more amide linkages have been replaced by ester linkages

Figure 1. Structure of romidepsin

Characterisation data were rather poor but it appears that romidepsin does not form salts and has a fairly low solubility in water, probably independent of pH. It is more soluble in organic solvents.

The drug substance is produced by fermentation and is purified by standard chromatographic and recrystallisation processes. It is enantiomerically pure.

There are a number of related species produced in the fermentation which are controlled to acceptable limits in the purified drug substance.

Several questions in relation to the chemistry and quality of the drug substance were raised with the sponsor. Details of these are beyond the scope of the AusPAR. However, it should be stated that a tighter limit is recommended for an unidentified impurity in drug batches used to make injection for Australia.

Drug product

Celgene proposes registration of a composite pack with two vials, a powder for concentrated injection and a diluent vial. Romidepsin 10 mg powder is formulated with povidone and hydrochloric acid (as required for pH for optimum stability). The diluent vial contains 2 mL of a mixture of propylene glycol and anhydrous ethanol. Addition of this diluent gives a colourless concentrated solution (romidepsin 5 mg/mL) which is further diluted with 500 mL of 0.9% sodium chloride solution before infusion.

The proposed dose is 14 mg/m² administered IV over a 4 h period on Days 1, 8, and 15 of a 28-day cycle. Hence the maximum daily dose is about 30 mg/day (3 vials for body surface area (BSA) 2.1 m²).

Povidone (also known as polyvinylpyrrolidone or PVP) is a polar, water-soluble polymer. It is used as a bulking agent to assist the lyophilisation process. Celgene claims that the povidone used is readily cleared renally. Povidone is not a common injection excipient but it is used in at least two other products for injection registered currently in Australia.

Propylene glycol is a more common injection excipient. At the maximum daily Istodax dose (approximately 3 vials), 5.0 g of propylene glycol and 1.2 mL ethanol would be infused.

The possibility of formulating a powder giving a simple aqueous infusion (30 mg dose would dissolve in approximately 100 mL) was not addressed in the submission. Aqueous solutions cannot be directly marketed because of degradation, apparently due to oxidation.

The powder for injection is made by lyophilisation of an acidified solution in *tert*-butyl alcohol and water. The *tert*-butyl alcohol is largely removed in the lyophilisation process but the limit for residues could be tightened (given batch data) and this is recommended toxicologically (see under *Nonclinical* section below).

No changes have been found on storage of the product, except for slight sensitivity to light.

The composition of the drug product has remained the same throughout clinical development and commercial production.

Sterility and endotoxin aspects are acceptable.

Several questions in relation to the chemistry and quality of the product were raised with the sponsor. Details of these are beyond the scope of the AusPAR.

Biopharmaceutics

No bioequivalence studies were submitted since the drug product is administered intravenously (IV).

Advisory committee considerations

The submission was considered at the 149th (2013/1) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommendation was as follows:

1. The PSC endorsed all the questions raised by the TGA in relation to the quality and pharmaceutical aspects of the submission by Celgene Australia Pty Ltd to register Istodax powder for injection containing 10 mg of romidepsin and agreed that they need to be answered to the satisfaction of the TGA.
2. The PSC advised the TGA that the level of propylene glycol in this product that is administered by IV infusion, in accordance with the dosage and administration regimen, is acceptable.
3. The PSC advised that the amendments to the PI be considered by the TGA.²
4. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the ACPM.

Quality summary and conclusions

Questions raised with the sponsor were answered adequately. There are no outstanding issues.

As noted above, a tighter limit is recommended for an unidentified impurity in drug batches used to make injection for Australia and a tighter limit is recommended for residual *tert*-butyl alcohol. A requirement for tighter limits could be made a condition of registration.

Registration is otherwise recommended with respect to chemistry and quality control aspects.

Updated conclusions

Prior to the final decision on this application the sponsor agreed to tighten the limits for the unidentified impurity and for *tert*-butyl alcohol. The revised limits were acceptable from a quality viewpoint.

Registration without conditions of registration was recommended with respect to chemistry and quality control aspects.

² Details of recommended revisions to the PI are beyond the scope of the AusPAR.

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

All pivotal toxicity studies were conducted in compliance with good laboratory practice (GLP) guidelines. The characterisation of pharmacokinetics (PK) of romidepsin was limited by the low doses used and the low sensitivity of the analytical methods in the early non-GLP studies. The major limitation of the toxicology program was that high doses could not be tested as romidepsin was acutely toxic to all species at doses close to the clinical dose of 14 mg/m². There was some evidence in the studies that organ systems other than those identified as major toxicity targets were affected by romidepsin. These potential toxicities were not investigated due to the early death of animals at doses close to the expected clinical exposure and the short-term nature of the toxicity studies. Another deficiency of the application is the lack of *in vivo* investigation of metabolism in either dogs or humans. The *in vitro* data to some extent provides a picture of the metabolic profile of romidepsin but it would be useful to have a characterisation of the species generated in living individuals. There appeared to be no investigation of metabolites in the clinical data which itself relied on the *in vitro* metabolic data.

Pharmacology

Primary pharmacology

Romidepsin has been identified as a histone deacetylase (HDAC) inhibitor. Histones play important roles in gene expression and post-translational modification of cellular proteins. The ability of romidepsin to inhibit the growth of malignant tissues is thought to be related to its ability to interfere with these processes.

Romidepsin shows different inhibition potency against the different classes of HDAC enzyme. Romidepsin is most potent against Class 1 HDACs with 50% inhibitory concentration (IC₅₀) values in the picomolar range (2-4 pM) against HDAC1 and HDAC2 and 0.15 nM against HDAC3 and HDAC 8 (all are Class 1 HDACs), while the expected clinical maximum concentration (C_{max}) is approximately 700 nM (377 ng/mL). The IC₅₀ values against Class 2 HDACs (HDAC 4, 5, 6, 7, 9) are in the nano- to micromolar ranges (21-1250 nM).

Evidence was provided for the modulation of a number of genes involved in tumour progression, including up regulation of p21^{WAF1/Cip1} and gelsolin and down regulation of vascular endothelial growth factor (VEGF) and c-myc. Some links between these changes in gene expression and the susceptibility of different tumours to inhibition by romidepsin was explored. There were some suggestive findings: for example, a romidepsin susceptible prostate tumour cell line had relatively lower basal levels of expression of p21^{WAF1/Cip1} and higher basal levels of expression of c-myc than a romidepsin insensitive renal tumour line, and exposure to romidepsin caused an increase in expression of p21^{WAF1/Cip1} only in the prostate tumour cells. The *in vitro* effects on gene expression occurred at a concentration (9.25 nM) well below the expected clinical exposure (700 nM). It is not clear whether these effects of romidepsin occur generally; multiple mechanisms are almost certainly involved in the anti-tumour effects of romidepsin.

Studies submitted by the sponsor provide good evidence that romidepsin inhibits the growth of a variety of solid and diffuse haematological tumours (including lymphoma) *in vitro* at nanomolar concentrations. Treatment of cell lines with romidepsin caused cell

cycle arrest and induced apoptosis. Romidepsin suppressed VEGF messenger ribonucleic acid (mRNA) expression of prostate cancer PC3 cells but not renal cell carcinoma ACHN cells, and basic fibroblast growth factor (bFGF) mRNA expression of both cell lines. IC₅₀ values for inhibition of tumour lines *in vitro* ranged from 0.3 ng/mL (0.56 nM) in the most susceptible lines to 5 ng/mL (9.25 nM) in resistant lines. IC₅₀ values for inhibition of non-malignant cells ranged from 3.2 ng/mL (5.92 nM) in NIH/3T3 mouse embryonic stem cells to >1000 ng/mL (> 1.9 mM) for normal human fibroblasts. Romidepsin produced tumour inhibition *in vitro* at a concentration well below the expected clinical C_{max} (700 nM).

The efficacy of romidepsin against a variety of human tumour xenografts in mice was investigated using various dose and schedule combinations. Romidepsin produced 131% growth delay of MX-1 breast tumour at a dose of 2.4 mg/kg (7.2 mg/m²) with a dosing schedule of once every 7 days for a total of 3 doses (Q7D x 3), which was approximately half the proposed clinical dose of 14 mg/m² with the same dosing schedule. Romidepsin produced 98% suppression of prostate (PC-3) growth at a dose of 3.2 mg/kg (9.6 mg/m²) with a more frequent dosing schedule of once every 4 days for a total of 3 doses (Q4D x 3).

It was reported that romidepsin resistance was rapidly induced in a colon carcinoma cell line (HCT15R) *in vitro*, and the induction of p-glycoprotein (P-gp, a transport protein) was shown to be responsible for the resistance. The up-regulated P-gp expression decreased slowly after cessation of romidepsin treatment, with ABCB1 as the gene responsible for the resistance. Multidrug resistance-associated protein 1 (MDRP1) was not up-regulated in the resistant cell line although romidepsin was shown to be transported by MDRP1. The cell line was also cross-resistant to paclitaxel and doxorubicin, which are well known P-gp substrates. The transport of romidepsin via P-gp was shown to be readily inhibited by cyclosporine A, a P-gp inhibitor. Since P-gp is linked to multidrug resistance, romidepsin treatment might induce multidrug resistance in cancer patients.

Secondary pharmacodynamics and safety pharmacology

A screen of 62 receptors and ion channels *in vitro* found that romidepsin interacted significantly with only two receptors: oestrogen and neurokinin₂ (NK₂) receptors. Romidepsin inhibited binding to the oestrogen receptor marginally at 1 µg/mL (27% for oestrogen and 16% for NK₂) and significantly reduced binding to both receptors at 10 µg/mL (98% for oestrogen and 71% for NK₂). Clinical exposures (C_{max} 700 nM or 377 ng/mL) are below the concentrations producing these effects, but atrophy of reproductive organs observed in the toxicity studies (see below) might be mediated by the inhibitory activity of romidepsin on the oestrogen receptor. NK₂ are expressed in a wide range of tissues, particularly gastrointestinal, respiratory, urinary and central nervous systems (Fattori *et al.*, 2004³). There were no nonclinical or clinical findings suggesting adverse effects or toxicity mediated by the inhibitory activity of this receptor. Furthermore, romidepsin has very limited distribution to the central nervous system (CNS), suggesting the low likelihood of CNS toxicity.

Specialised safety pharmacology studies covered the cardiovascular, CNS and respiratory systems. The CNS study looked at the effects of a single 4 h infusion in rats. Animals showed signs of generalised CNS depression (reduced activity, reduced reflexes, reduced grip strength) at 0.3 mg/kg and 1.0 mg/kg. The higher dose (1.0 mg/kg) was lethal to 3/6 animals within 24 h of dosing. Given the very low distribution to CNS, the CNS clinical signs observed in the safety pharmacology study were probably due to general toxicity of the drug.

³ Fattori D, Altamura M and Maggi CA (2004). Small molecule antagonists of the tachykinin NK₂ receptor. *Mini-Review in Medicinal Chemistry* 4: 331-340.

Cardiovascular effects were evaluated *in vitro* and *in vivo*. *In vitro* romidepsin suppressed the current in human ether-a-go-go related gene (hERG) channels by 37% at 10 µg/mL in HEK293 cells. Romidepsin also reduced action potentials amplitude from 131.3 ± 0.4 to 126.8 ± 0.7 mV and shortened the action potential duration at 90% repolarisation (APD₉₀) from 192.8 ± 8.1 to 169 ± 6.8 ms in guinea-pig papillary muscle at a concentration of 10 µg/mL. The only notable effect on cardiac function observed in dogs *in vivo* in the safety pharmacology study was a small increase in heart rate in dogs following a 4 h infusion of 1 mg/kg (C_{max} from study GLR040231 with the same dose and infusion period was 182 ng/mL). Small (<10%) increases in QTc⁴ in the same study were only apparent using Bazett's and Frederica's QT interval correction formulas and were not significant. In one repeat dose toxicity study in dogs prolongation of QTc intervals (by 23% compared with the control group) was observed 24 h after a 4 h infusion at 1.0 mg/kg (one dose per week), and the effect was not apparent after 2 weeks recovery. The plasma romidepsin concentration in dogs at 1 h was 146-218 ng/mL, below the clinical C_{max} (377 ng/mL). One study reported sub-epicardial haemorrhages in the hearts of 3 dogs (two given 2.0 mg/kg twice weekly for a total of four doses (2W x 4), and one given 1.0 mg/kg Q7D x 4). One rat study reported elevated lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) consistent with some heart damage in rats given 0.01 mg/kg on a 4 week once daily (QD) schedule but there was no corresponding histopathology. Chronic focal inflammation and neutrophilic cellular infiltration of the heart occurred in some mice given various doses and schedules but results on LDH and CPK levels were inconclusive because of small numbers. In a study on cardiac myocytes in culture romidepsin was toxic to rat, dog and human cells at doses from 0.1 µM. Although limited, there is some evidence suggesting potential for cardiotoxicity in humans.

Pharmacokinetics

Pharmacokinetic (PK) studies were conducted in rats and dogs using IV administration as either bolus or infusion. Single and repeat-dose studies were conducted in both species. Time to reach maximum concentrations (T_{max}) values corresponded to either the first plasma sample following IV bolus or generally the first sample following the cessation of an infusion. Romidepsin was rapidly distributed and plasma values declined steeply after a bolus injection or at the end of infusion. After a bolus dose of romidepsin in rats half life (t_½) estimates ranged from 0.2 to 0.9 h. Following 4 h infusion in dogs romidepsin appeared to have a slightly longer terminal t_½ (< 2 h) than that seen in rats (IV bolus).

Exposure in terms of C_{max} and area under the concentration-time curve (AUC) increased in a dose proportional manner in the 26 week repeat-dose experiments in rats at 0.1-1.0 mg/kg. C_{max} and AUC values were higher in Week 26 than in Week 1. This may suggest a change in penetration into peripheral tissues or metabolism but this was not investigated.

Romidepsin distributed widely and rapidly into tissues with peak values at 5 min (first sampling time) post-dose. The highest concentrations were found in the kidneys, although little preferential distribution to any target organ was seen. Concentrations were high in urinary bladder, jejunum, liver, and adrenal gland, low in white fat, eye ball and thigh bone, and very low in brain and testes. This indicates that the distribution to brain tissues was limited. Romidepsin (measured as radioactivity) appeared to some extent to be retained in blood, compared to plasma, in the rat mass balance experiment although metabolites may account for the result.

⁴ QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is QT interval corrected for heart rate.

Protein binding of romidepsin was highest in humans (around 93%), slightly less in dogs (87%) and low in rats (38%). The percentage bound in rat serum showed little change with increasing concentration while in dogs and humans the value dropped by around 10% when the concentration reached 5000 ng/mL. In human serum and plasma the percentage bound was 92-94% at 50-1000 ng/mL which includes therapeutically relevant concentrations (human C_{max} = 377 ng/mL). The investigation of romidepsin binding to human serum albumin and alpha1 acid glycoprotein (α 1-AGP) showed that binding to α 1-AGP (93.5%) was much greater than that to albumin (19.9%). This suggests that α 1-AGP is the principal binding protein in human serum.

No *in vivo* metabolism data from humans or dogs was available. Experiments *in vitro* using liver microsomes showed a higher rate of romidepsin metabolism in liver microsomes from humans compared to rats and dogs. However, similar patterns of metabolism in terms of metabolite species produced were seen in rat, dog and human liver microsomes *in vitro*. Romidepsin was shown to be a substrate for cytochrome P450 (CYP) 3A4, which was identified as the primary enzyme for the metabolism of romidepsin. All metabolites detected in human hepatic microsomes were also detected in rat and/or dog microsomes. Romidepsin was metabolised to more than 10 detectable metabolites with no predominant metabolite species. In an *in vivo* study in rats 30 putative metabolites were detected. The structures of 28 metabolites from either *in vitro* experiments in rats and humans or *in vivo* rat experiments were elucidated. Metabolite M1 was shown to be the reduced form of romidepsin (reduction of the disulphide bond to thiols) produced non-enzymatically and can be produced via reaction with glutathione. M11 and M12 were also found to be able to be non-enzymatically produced. Production of most metabolites was mediated via nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) dependent enzymatic reactions in all species.

Romidepsin and its metabolites were shown to be excreted predominantly in faeces via the biliary route in rats. Urinary excretion was a secondary route accounting for approximately 16% while faeces accounted for approximately 75% in the mass balance study. Both unchanged compound and metabolites were excreted in urine and faeces. In urine the parent drug predominated but accounted for less than 5% of the administered dose. In bile and faeces the parent compound was not the predominant species, accounting for 3% of administered radioactivity in bile. Metabolites MH-10, MH-5, and MH-21 each accounted for just over 4% in bile and all metabolites except MH-21 (3.9%) accounted for < 3% of dose in faeces.

The PK profiles of rats and dogs were similar. Some differences noted between the species may have been due to differences in the method of administration (4 h infusion versus IV bolus). The *in vitro* metabolic profiles of rats, dogs, and humans were quite similar with all metabolites detected in human microsomes also detected in rat and/or dog microsomes. This supports the use of these animals for the toxicological investigation of romidepsin. The lack of *in vivo* investigation of metabolism in either dogs or humans is considered a deficiency of the application. The *in vitro* data to some extent provides a picture of the metabolic profile of romidepsin but it would be useful to have a characterisation of the species generated in living individuals. There appeared to be no investigation of metabolites in the clinical data which itself relied on the non-clinical metabolic data.

Pharmacokinetic drug interactions

Since romidepsin is predominantly metabolised by CYP3A4, inhibitors of this enzyme may increase plasma romidepsin concentrations.

Romidepsin was able to inhibit the metabolic activity of several CYP isoforms *in vitro* at high concentrations (>10 μ M). However at 1 μ M only CYP2E1 and CYP3A4 activities were reduced by around 5%. Romidepsin is unlikely to cause significant CYP inhibition.

Romidepsin showed weak inductive ability for CYP1A2 (enzyme activity: 2.3 fold at 0.5 μ M

and 3.8 fold at 2 μ M, compared with 34 fold for the positive control, omeprazole; mRNA expression: 23 fold at 2 μ M, compared with 1105 fold for omeprazole). CYP2B6 and 3A4 were also examined but were not induced by romidepsin.

Romidepsin was shown to be a substrate for P-gp and MDRP1 in published studies. Tissue distribution and elimination of romidepsin may be altered by P-gp or MDRP1 inducers or inhibitors.

Romidepsin is not a P-gp inhibitor. Increased P-gp expression has been demonstrated in cells exposed to romidepsin. The potential for P-gp induction and consequent changes in the exposure to romidepsin and other P-gp transported drugs should be considered.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in rats and dogs. The clinical route (IV) was used together with an observation period of 14 days in accordance with the EU guideline for single-dose toxicity. The doses tested (up to 5.1 mg/kg in rats and 1.0 mg/kg in dogs) were, however, generally below doses which would be expected to generate plasma concentrations above those attained clinically. Higher doses were tested in dogs in repeat dose studies (see below).

In acute toxicity studies in rats the maximum non-lethal dose was 2.6 mg/kg (15.6 mg/m²) by 30 sec IV infusion; in dogs the maximum non-lethal dose was 1.0 mg/kg (20 mg/m²), highest dose tested in the single dose study. In some repeat-dose toxicity studies 1.0 mg/kg by infusion over 30 sec (dogs) or infusion over 4 h (rats) was lethal to both species. In dogs, irregular heart rate, shallow and jerky respiration, tremor and decreased body surface temperature were observed at 1.0 mg/kg immediately after dosing, and vomiting on the following day. Pathological changes seen in rats following lethal doses (3.6 and 5.1 mg/kg by 30 sec IV infusions) in rats in the acute toxicity studies were found principally in the thymus (clouding of the thymic parenchyma, dark red foci) and the lungs (dark red colouration). Atrophy of the thymus was the only pathological finding in the dog study.

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in three species: mouse, rat and dog. The maximum doses employed in these studies were 8.0 mg/kg/dose in the mouse, 1.67 mg/kg/dose in the rat and 2 mg/kg/dose in the dog. Only one study lasted beyond 4 weeks and this was a 26-week rat study using the proposed clinical dose schedule and IV bolus injection. The other studies in rats and dogs employed a number of different dose schedules and used bolus dosing as well as infusion. Many were part of a program to optimise the dosing method, serving as dose range-finding studies. Several of these studies used very small numbers of animals, as low as 1/sex/group (dog studies). This meant that comparisons of pathology at the end of the dosing period and the end of recovery used a single animal of a different sex in each case. The animal studies appeared to have predicted clinical toxicity in patients.

Relative exposure

Exposure ratios are calculated based on animal:human AUC or C_{max} . In humans AUC over time zero to infinity ($AUC_{0-\infty}$) was used, while in rats $AUC_{0-\infty}$ and in dogs AUC over time zero to 24 h ($AUC_{0-24 h}$) values were reported. A limitation of the kinetic data was that AUCs could not be calculated in the preliminary repeat-dose dog experiments due to low sensitivity of the early analytical method (limit of quantitation (LoQ) 198 ng/mL) and insufficient data (plasma concentrations <LoQ 10 – 20 min after infusion). Plasma drug

concentrations were not measured in the pivotal 4-week dog study, but PK data in a single dose 4 h infusion study using the same doses provided evidence of drug exposure in dogs. Exposure ratios based on animal:human plasma C_{max} are included due to the limited number of AUC values. A Phase II study (NCI 1312) using the proposed dose regimen of 14 mg/m² administered on days 1, 8, and 15 every 28 days was used for human exposure estimates. The C_{max} was 377 ng/mL (n = 94) and the AUC_{0-∞} was 1549 ng.h/mL (n = 59).

Table 1. Relative exposure in single and repeat-dose toxicity studies

Species/Study	Sampling time	Dose (mg/kg)	AUC (ng·h/mL)	C_{max} (ng/mL)	Exposure ratio*	
					AUC	C_{max}
Rat (CrI:CD) 501650 (26 weeks, IV bolus Q7Dx3/month)	Day 176	0.1	4.69 ^a	8.63	0.003	0.02
		0.33	24.6 ^a	34.6	0.02	0.09
		1.0	80.1 ^a	130	0.05	0.34
Dog (Beagle) GLR030590 (Q7D x 3)†	Day 1 (4 h Infusion)	0.3	153.3 ^b	46.1	0.1	0.12
		1.0	562.6 ^b	182	0.36	0.48
Dog (Beagle) Study SRI-Chm-93- 2-6464-XCV (non- GLP) (3 doses on Days 1, 12, 19)	Day 1 (30 sec injection)	0.5	-	2477	-	6.6
		1.0	-	2475	-	6.6
		2.0	-	2785	-	7.4
	Day 19 (1 h infusion)	0.5	-	334	-	0.9
		1.0	-	390	-	1.0
		2.0	-	403	-	1.1
Dog (Beagle) SRI-Chm-93-3- 6464-XCVI (Q7D x4 or 2W x4)	Day 22 (1-1.5 h infusion; Q7Dx4)	0.5	-	424	-	1.1
		1.0	-	847	-	2.3
		2.0	-	1172	-	3.1
	Day 25 (1- 1.5 h infusion; 2Wx4)	0.5	-	508	-	1.4
		1.0	-	717	-	1.9
		2.0	-	1139	-	3.0
Human NCI 1312 (patients with T cell lymphoma)	Day 1 (4 hr infusion)	14 mg/m ²	1549 ^a	377	-	-

Species/Study	Sampling time	Dose (mg/kg)	AUC (ng·h/mL)	C _{max} (ng/mL)	Exposure ratio*	
					AUC	C _{max}
(Q7D x3/4W cycle)						

^aAUC_{0-∞}; ^b AUC_{0-24h}; † Based on PK data from a single dose study (GLR040231); * Animal:human AUC or C_{max} of total drug in plasma. The exposure ratios would be approximately 10-fold higher for rats and 2-fold higher for dogs based on free fraction of romidepsin in plasma (free fraction in rat, dog and human plasma: 0.62, 0.13 and 0.06, respectively). Q7Dx3: every 7 days for a total of 3 doses; Q7D x4 : every 7 days for a total of 4 doses; 2W x4: twice weekly for a total of 4 doses; Q7D x3/4W cycle: every 7 days for a total of 3 doses in a 4 week cycle .

On the basis of AUC_{0-∞} or AUC_{0-24h} the exposure levels achieved in experimental animals were very low, reaching a maximum exposure ratio of 0.4 based on a single 4 h infusion dose of 1 mg/kg in male beagle dogs (n=3) and only 0.05 in the pivotal 26-week rat study. If C_{max} values are compared, a maximum ratio of about 7 was achieved in dogs after a bolus IV dose of 2 mg/kg and 3 after 1-1.5 h infusion of the same dose. Generally romidepsin was not well tolerated by rats or dogs which constrained the safety margin for the proposed clinical dosing regimen. The exposure comparison was based on total drug in plasma. Based on the free fraction of romidepsin in plasma, the exposure ratios would be approximately 10-fold higher for rats and 2-fold higher for dogs (free fraction in rat, dog and human plasma: 0.62, 0.13 and 0.06, respectively).

Major toxicity

The target organs observed with romidepsin were the haematopoietic system including lymphoid tissues and bone marrow, the site of injection, reproductive organs and gastrointestinal tracts. There were also inconsistent reports of lesions in the heart (see *Safety Pharmacology* above). Lesions in other organs were reported in some animals in different studies but because of the small numbers of animals and the variations in dose schedule and vehicles used the significance of these is uncertain.

Effects on the haematopoietic system were seen in all species regardless of dose or dose schedule. Total white blood cells (WBC) were consistently decreased by romidepsin in rats and dogs. The decrease was not seen in all WBC types: lymphocytes were consistently reduced but neutrophils were generally increased. One study in mice reported overall increases in WBCs. Red cell parameters and platelets were also generally decreased by romidepsin. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were generally increased. Effects on haematological parameters were most pronounced immediately after dosing and generally recovered between doses when the once every seven day (Q7D) schedule was used and at the end of the dosing period. Romidepsin also caused histopathological changes in all major organs of the haematopoietic system. Romidepsin-related toxicities observed consistently in the rat included lymphoid cell depletion in the lymph nodes, spleen and thymus and depletion of haematopoietic cells in the bone marrow at all doses. Exposure ratios for the lowest dose (0.1 mg/kg) were 0.003 based on AUC. Similar observations were made in the dog at all doses down to 0.3 mg/kg (4 h infusion Q4D). Exposure ratios for the lowest dose were 0.1 based on AUC in the single dose 4 h infusion study at 0.3 mg/kg and about 1 based on C_{max} in the dose range-finding studies by 1-1.5 h infusion at 0.5 mg/kg. Romidepsin was an inhibitor of the growth of bone marrow progenitor cells from mice, dogs, and humans with IC₅₀ values of 1.0, 0.35, and 0.03 nM, respectively, considerably lower than the clinical C_{max} of 700 nM.

The sponsor states that these (and other) changes were fully reversible but this is not supported by the data. For example in the 1-1.5 h infusion study in dogs with a 4-week recovery period (Study no. SRI-Chm-93-3-6464-XCVI), anaemia, splenic necrosis and depletion, thymic depletion persisted in a male dog to day 50 (4 weeks after the last dose).

Some caution is required, however, as only a single animal from each dose/schedule was retained to the end of the recovery period in this study. All histopathological changes persisted for the 4 week recovery period in a dog given 3 doses of 1.0 mg/kg every 4 days (Q4D), but again in this study only a single animal was evaluated. In the only chronic (26-weeks) toxicity study in rats, no animals were retained for recovery so how reversible effects are after repeated dose cycles is not known. A reasonable conclusion is that the severity of the effects on the haematopoietic system is reduced over time but the possibility of irreversible changes has not been ruled out. A similar caveat applies to the other effects of romidepsin seen in animals.

Gastrointestinal effects in the dog were characterized by emesis and bloody diarrhoea and histopathological changes were seen in the stomach and intestines including haemorrhage, degeneration and necrosis of the mucosa. No comparable effects were seen in either mice or rats although both these latter species showed consistent weight loss during dosing with romidepsin.

Atrophy of reproductive organs (mammary gland, ovary, vagina, and uterus) in female rats occurred at all doses (>0.1 mg/kg/week, exposure ratio (ER) 0.003 based on AUC) and prostate and/or testes in male rats at > 0.33 mg/kg/week (ER 0.02 based on AUC) or 0.1 mg/kg/day (ER 0.02 based on AUC by weekly dosing) and male dogs at all doses (>0.3 mg/kg/week, ER 0.1 based on AUC). Testicular degeneration was also observed in mice receiving 3.6-8 mg/kg romidepsin. Several studies in different species indicated that these changes reversed slowly if at all. For example, no recovery of the testicular lesions in mice was observed 4 weeks after the last dose of romidepsin. The effects on reproductive organs might be partly attributable to the inhibitory activity of romidepsin on the oestrogen receptor.

Consistent changes in clinical chemistry were increases in alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and fibrinogen in both rats and dogs. Increases in cholesterol, creatine kinase (CK), and LDH, and decreased blood urea nitrogen (BUN) and electrolytes were also seen in some studies in both species. These changes were not clearly linked to underlying organ pathology. Abnormal pathological findings in the liver, described as focal and centrilobular hepatocellular necrosis, biliary hyperplasia and extramedullary haematopoiesis, were reported in one study in the rat at all doses (0.1-1.0 mg/kg/day) which employed daily IV bolus dosing for two weeks.

Effects at the injection/infusion sites are discussed below (see *Local tolerance*).

Genotoxicity and carcinogenicity

The potential genotoxicity of romidepsin was investigated in the standard battery of tests. All assays were appropriately validated and the conduct of the studies was in accordance with the relevant regulatory guidelines. Romidepsin was negative in the bacterial mutagenicity assay at concentrations up to the limit of solubility. The results were negative in the rat micronucleus test at doses up to the maximum tolerated dose (MTD) in the rat (1 mg/kg in male rats, and 3 mg/kg in female rats). In the mouse lymphoma forward mutation assay romidepsin gave equivocal results in some experiments and weakly positive results in others. Although the increases in mutation frequency were statistically significant, the increases were small and their biological significance is doubtful. The balance of evidence indicates that romidepsin is unlikely to be genotoxic.

No carcinogenicity studies were conducted, which is considered acceptable given the expected short life expectancy of the target patient group⁵.

Reproductive toxicity

There were no fertility studies. Information on the effects of romidepsin on reproductive organs comes from the general toxicity studies. Toxicity to male and female reproductive organs was reported in all the species used in the main toxicity studies (mouse, rat and dog). Consistent observations were atrophy of the testes and ovaries with similar effects seen in other reproductive organs (uterus, vagina, mammary glands, prostates and seminal vesicles). Romidepsin treatment is likely to adversely affect male and female fertility in patients.

Embryofetal development studies were conducted in one species (rat) which is acceptable for an anticancer agent⁵, as these studies showed clear evidence of embryo-lethal and teratogenic effects. Rats received daily doses of up to 0.5 mg/kg/day romidepsin during organogenesis. The doses were limited by the acute toxicity of romidepsin to pregnant females. The exposures were below the expected clinical exposure (see table below). The toxicity to fetuses at very low exposures indicated that romidepsin should not be used in pregnancy.

Table 2. Relative exposure in pregnant rats

Species	Sampling time	Dose (mg/kg/day)	AUC _{0-24h} (ng·h/mL)	C _{max} (ng/mL)	Exposure ratio	
					AUC*	C _{max}
Rat (CrI:CD (SD))	GD 17	0.1	2.44	6.64	0.01	0.02
		0.2	4.99	14.5	0.02	0.04
		0.5	17.2	44.5	0.08	0.12
Human (patients with T cell lymphoma)	Day 1	14 mg/m ²	1549 [#]	377	-	-

[#] AUC_{0-∞}; * Rat AUC_{0-24h} x 7: human AUC of total drug in plasma. The exposure ratios would be approximately 10-fold higher. GD: gestation day

Romidepsin caused almost complete fetal loss (97%) in dams dosed at 0.5 mg/kg/day. Surviving fetuses showed rotated hindlimbs and folded retina, which were also seen in fetuses from dams receiving 0.2 mg/kg/day. Fetuses from these dose groups also had ossification delay (caudal vertebrae, metatarsals and/or hindlimb phalanges) and increased supernumerary thoracic ribs (high dose only). Maternal and fetal weights in all treated groups were significantly lower than those of the control group.

Pregnancy category

The sponsor has proposed Pregnancy Category D⁶, which is consistent with the findings in rats.

⁵ Regulatory guidance: (EMA/CHMP/ICH/646107/2008; ICH Topic S9 *Nonclinical Evaluation for Anticancer Pharmaceuticals*)

Local tolerance

Romidepsin was negative in a dermal irritation test in rabbits but was identified as a skin sensitiser in mice at a topical concentration of 0.1% (in acetone:olive oil) in the mouse local lymph node assay.

Dose-related local reactions (oedema and erythema) at the injection sites were reported in all species tested. A consistent finding in the repeat dose toxicity studies was inflammation and necrosis at the catheter site which persisted for up to 4 weeks after dosing had ceased. In a dose range-finding study in dogs, dose-related swelling and inflammation of the legs were observed at the injection sites after the first dose. A subsequent skin test showed oedema and erythema by both romidepsin and vehicle (ethanol/propylene in saline), but not saline. While the intradermal tests in the dog study suggest irritation by the dosing vehicle, local swelling and erythema in the dog study were dose-related, and similar effects at the injection site were also seen in other dog studies and in mice and rats, indicating that romidepsin is irritating to soft tissues. Caution should be exercised when administering romidepsin to patients to avoid extravasation.

Impurities

tert-Butyl alcohol (TBA) is a residual solvent present in the drug product. A quality control specification for TBA was nominated by the sponsor.

tert-Butyl alcohol is not listed in the ICH Q3C guidance⁷ as a residual solvent but several other small aliphatic alcohols are included in the guidance with permitted daily exposure (PDE) of 30 mg/day (methanol, a Class 2 solvent) or 50 mg/day (1-butanol, 2-butanol, ethanol, 3-methyl-1-butanol, 2-methyl-1-propanol, 1-pentanol, 1-propanol, 2-propanol; all are Class 3 solvents). *tert*-Butyl alcohol is also a major metabolite of *tert*-butyl methyl ether (Amberg *et al.* 2001⁸), also a Class 3 solvent with a PDE of 50 mg/day.

The main safety issue with TBA is potential toxicity to the kidney and urinary bladder based on findings in female rats (described below). The local effects at the injection site observed in IV studies in rats are not of safety concern because of the low level present in the drug product and further dilution of the product in an infusion solution.

A risk assessment by the National Sanitation Foundation (NSF) Toxicology Services, USA established an oral reference dose (RfD) for TBA of 1 mg/kg/day based on renal effects in female rats in a chronic study (NSF Toxicology Services, 2003⁹). The oral RfD (7 mg/kg/week) is 140 times the expected maximum clinical exposure to TBA from Istodax. Since patients would be exposed to TBA by the IV route, the IV toxicity study is considered more relevant to the risk assessment of TBA present in Istodax. The short term repeat dose IV study in rats showed renal and bladder effects in female rats at all dose levels (5-500 mg/kg/week). The lowest dose adjusted for body surface area (30 mg/m²) in rats is approximately 18 fold higher than the expected maximum exposure to TBA in patients (1.68 mg/m²). The sponsor has also assessed the risk of TBA based on clinical studies with romidepsin batches containing TBA, which will need to be reviewed by the clinical evaluator.

While the exposure margin is small, the risk of potential adverse effects on kidney and urinary bladder to patients may be outweighed by the benefit of romidepsin or justified by

⁶ Category D is defined as: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

⁷ ICH Guideline Q3C (R5) on impurities: guideline for residual solvents EMA/CHMP/ICH/82260/2006

⁸ Amberg A, Rosner E, & Dekant W. Toxicokinetics of methyl *tert*-butyl ether and its metabolites in humans after oral exposure. *Toxicol Sci.* 2001; 61 (8):62-67.

⁹ NSF Toxicology Services (2003). *t*-Butanol CAS # 75-65-0: oral risk assessment document. NSF International, Ann Arbor, MI, USA. <<http://www.nsf.org/>>

clinical data. In any case, the level of TBA in romidepsin should be reduced to as low as possible. In the sponsor's assessment of TBA, it is indicated that the specification for TBA in Istodax in the US is less than the limit proposed in the Australian product.

Paediatric use

Romidepsin is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the safety specification of the risk management plan

Nonclinical safety concerns that have not been resolved by clinical data or are of unknown significance for romidepsin detailed in the sponsor's draft Risk Management Plan (RMP) dated 5 May 2012 are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- Pivotal studies were conducted in accordance with GLP guidelines. The nonclinical studies lacked *in vivo* metabolism studies in dogs (there was no human *in vivo* metabolism data either) and long term repeat dose studies in a non-rodent species. However, the available nonclinical toxicity studies appear to have predicted clinical adverse effects in patients.
- Non-clinical efficacy was extensively investigated in cancer cell lines and animal cancer models. Romidepsin is a HDAC inhibitor with high selectivity to Class 1 HDACs and IC₅₀ in the nanomolar range. Evidence was provided for the modulation of a number of genes involved in tumour progression including up regulation of p21^{WAF1/Cip1} and gelsolin and down regulation of VEGF and c-myc. Studies submitted by the sponsor provide good evidence that romidepsin inhibits the growth of a variety of solid and diffuse tumours (including lymphoma) *in vitro* at nanomolar concentrations (IC₅₀ values from 0.3 to 8.36 nM). Efficacy against tumour growth of human tumour xenografts (for example, breast cancer) in nude mice was also demonstrated.
- An *in vitro* study with a colon carcinoma cell line indicated that romidepsin induces drug resistance due to the up-regulation of P-gp (ABCB1 gene) expression. Since P-gp is linked to multidrug resistance, romidepsin treatment might induce multidrug resistance in cancer patients.
- A screen of 62 receptors indicated that romidepsin interacted with only oestrogen and neurokinin₂ receptors but only at concentrations above those expected clinically, but atrophy of reproductive organs observed in the toxicity studies might be partly related to the inhibitory activity of romidepsin on the oestrogen receptor. Animals showed signs of generalised CNS depression in CNS safety studies. Given the very low distribution to CNS, the CNS clinical signs observed in the safety pharmacology study were probably due to general toxicity of the drug. Cardiovascular safety studies were conducted *in vitro* and *in vivo*. The results of these and observations made in the repeat-dose toxicity studies in dogs suggest romidepsin has the potential to increase QT intervals and possible damage to cardiomyocytes.
- The disposition of romidepsin was biphasic with an initial rapid decline and a secondary elimination phase in both rats and dogs. Estimates of elimination half life following IV bolus in rats and at the end of a 4 h infusion in dogs were between 0.2 and 0.9 hs in rats and < 2 h in dogs. Distribution from the plasma was rapid and wide with highest penetration into kidney and lowest penetration into brain tissue. Plasma protein binding differs between species (approximately 38%, 87% and 94% in rat, dog and human plasma, respectively). *In vitro* experiments with human serum showed that

α 1-AGP is the principal binding protein. The characterisation of romidepsin PK was limited by the very rapid disappearance of romidepsin from the plasma and low sensitivity of the analytical method used in early studies.

- Metabolism was rapid in *in vitro* experiments using rat, dog, and human tissues, and no metabolite species predominated. Romidepsin is metabolised by CYP3A4 and non-enzymatic metabolism also occurs. Romidepsin was metabolised to more than 10 detectable metabolites with no predominant metabolite species. In an *in vivo* study in rats 30 putative metabolites were detected. In the rat mass balance study no metabolite accounted for more than 5% of the administered dose. Production of most metabolites was mediated via NADPH-dependent enzymatic reactions in all species. There were no *in vivo* metabolism data in dogs or humans, but the metabolic profiles in these species *in vivo* are not expected to be significantly different from the *in vitro* observations. Excretion of romidepsin was predominantly in faeces via the biliary route although some excretion in the urine was seen in the mass balance study. Both parent drug and metabolites were excreted via these routes but none accounted for more than 5% of the administered dose.
- Romidepsin is a substrate of P-gp and MDRP1, and also induces P-gp. This creates the potential for interactions with other drugs transported by these transporters. Cross resistance to paclitaxel and doxorubicin has been shown in cells with romidepsin induced P-gp. *In vitro* experiments suggest that α 1-AGP is the principal binding protein and low affinity for albumin was demonstrated.
- Romidepsin displayed a high degree of single-dose toxicity by the IV route with lethal doses close to the expected clinical dose in mg/m². This high acute toxicity constrained the toxicity program.
- Repeat-dose toxicity studies were conducted in mice, rats and dogs. Only one study in rats (26 weeks) lasted more than 4 weeks. Other repeat-dose studies examined only short periods of exposure (up to 4 weeks in mice and dogs). The animal studies appeared to have predicted clinical toxicity in patients. At doses below the expected clinical exposure romidepsin produced toxic effects in the haematopoietic system (leukopenia, lymphopenia, anaemia, thrombocytopenia, lymphoid depletion of lymphoid organs, and depletion of haematopoietic cells in the bone marrow) and in the reproductive organs of males and females (atrophy of reproductive organs) and inflammation and necrosis at the infusion site. The severity of these effects declined between doses and at the end of the dosing period but some effects persisted. There were also effects on the gastrointestinal system in dogs (emesis, diarrhoea, mucosal haemorrhage and degeneration or necrosis of stomach and intestines), and, less consistently observed, liver (elevated plasma ALT, AST and ALP in rats and dogs, focal and centrilobular hepatocellular necrosis, and biliary hyperplasia in rats by daily bolus dosing) and heart (chronic focal inflammation and neutrophilic cellular infiltration of the heart in mice only) damage.
- The potential genotoxicity of romidepsin was investigated in a standard battery of tests. The results were negative in the bacterial mutagenicity assay and the rat micronucleus test. Equivocal and weakly positive results were obtained in the mouse lymphoma forward mutation assay, but the balance of evidence indicates that romidepsin is unlikely to be genotoxic. No carcinogenicity studies were submitted, which is acceptable for the proposed indication.
- Reproductive toxicity studies were conducted in one species (rat) which showed clear evidence of embryo-lethal and teratogenic effects. There were no fertility studies, but repeat dose studies showed clear effects on male and female reproductive organs, indicating that the fertility of patients is likely to be compromised by treatment with romidepsin.

- Romidepsin was identified as a skin sensitiser in the mouse local lymph node assay, suggesting romidepsin may elicit allergic reactions of the skin from repeated dermal exposure. Dose-related local reactions (oedema, erythema, inflammation and necrosis) at the injection sites were reported in all species tested. Caution should be exercised when administering romidepsin to patients to avoid extravasation.
- In a short term repeat dose study with *tert*-butyl alcohol, which is a residual solvent in romidepsin, by IV injection, transitional cell hyperplasia and inflammation of renal pelvis and urinary bladder were observed at all doses. The lowest dose was only 18 times the maximum clinical exposure at the proposed limit and recommended clinical romidepsin dose of 14 mg/m². *tert*-Butyl alcohol at the proposed limit may cause adverse effects of the kidneys and urinary bladder in patients. The sponsor has provided clinical data to justify the TBA level in romidepsin. The proposed limit may be justified by clinical data or outweighed by the benefit of romidepsin. There may also be scope for reducing the limit of TBA.

Conclusions and recommendation

- The primary pharmacology studies demonstrated HDAC inhibition and anticancer activity at concentrations or doses lower than those expected clinically.
- Clinically relevant hazards identified in safety pharmacology were QT prolongation and oestrogen receptor inhibition.
- Major toxicities identified in nonclinical studies were to the haematopoietic system, the reproductive systems of males and females and lesions at the infusion site. There were also, less consistent, signals of liver and heart toxicity. All these effects occurred at exposure levels lower than the expected clinical exposure based on AUC or C_{max}.
- Romidepsin is unlikely to be genotoxic but the possibility cannot be eliminated. No carcinogenicity studies were performed, which is acceptable for the proposed indication.
- Romidepsin is embryolethal and teratogenic in rats, and fertility is likely to be affected in patients based on toxicity to the reproductive organs observed in repeat dose toxicity studies.
- There is a high likelihood of toxicity findings identified in the nonclinical studies to occur in patients treated with romidepsin. The application is approvable only if the adverse effects are clinically manageable.
- *tert*-Butyl alcohol (a residual solvent) at the proposed limit may cause adverse effects of the kidneys and urinary bladder based on animal studies. However, the proposed limit may be justified by clinical data or outweighed by the benefit of romidepsin. There may also be scope for reducing the limit of TBA.

Revisions to nonclinical statements of the draft PI were also recommended. Details of these are beyond the scope of the AusPAR.

IV. Clinical findings

Introduction

Clinical rationale

Peripheral T-cell lymphoma is a rare form of non-Hodgkin's lymphoma with many sub-types that share an aggressive clinical behaviour and a poor prognosis with high relapse rates following treatment. The overall incidence in Australia is approximately 10% of all lymphomas. Long term survival in patients with this disease is extremely poor with a five year overall survival rate of approximately 7-32% depending on the sub-type of PTCL.

First line therapy presently rests with the utilisation of CHOP¹⁰ type regimens either with or without consideration for subsequent high dose therapy and autologous stem cell infusions. For patients who relapse or are refractory there is no consensus on standard therapy.

The class of HDAC inhibitors are a novel class of anti-neoplastic drugs that exert their effects through modulation of gene expression. Acetylation of non-histone-proteins is also likely to be critically important. HDAC inhibitors have wide ranging effects on malignant cells and activity in various haematological malignancies including Hodgkin's lymphoma and CTCL.

Early Phase I/Phase II studies submitted for this application indicated activity for romidepsin in heavily pre-treated patients with relapsed or refractory PTCL, prompting initiation of further evaluation.

Scope of the clinical dossier

The clinical part of the dossier included full study reports for 8 PK and pharmacodynamics (PD) studies, the final report of the pivotal efficacy and safety Study GPI-06-0002, and the report of the supporting efficacy and safety Study NCI 1312-PTCL.

Paediatric data

Not relevant to this application.

Good clinical practice

All aspects of good clinical practice were observed in the pivotal and supportive study.

Pharmacokinetics and pharmacodynamics

Studies providing pharmacokinetics and pharmacodynamics data

The PK and PD of romidepsin have been evaluated in several Phase I and II studies involving subjects with various types of cancer including relapsed or refractory cancers. Doses in the various studies ranged from 1-24.9 mg/m² infused for 4 h on Days 1 and 5 every 21 days, and 14mg/m² infused for the same duration on Days 1, 8 and 15 every 28 days. A summary of the submitted PK/PD studies is shown in Table 3.

¹⁰ Cyclophosphamide/hydroxydaunomycin (doxorubicin)/Oncovin (vincristine)/prednisone

Table 3. Summary of clinical studies and analysis

T-95-0077	Pharmacokinetic report: Phase 1 trial of a 4-hour infusion of depsipeptide (NSC630176) given on days 1 and 5 of a 21-day cycle in patients with refractory neoplasms
T-95-0022	Pharmacokinetic report: Phase 1 trial of a 4-hour infusion of depsipeptide given on days 1, 8, and 15 of a 28-day cycle in patients with advanced cancers, solid tumors
AN10018a	Development of a non-compartmental model pharmacokinetics of romidepsin and assessment of dose proportionality
NCI 1312 (Protocol 01-C-0049)	Non-compartmental pharmacokinetics of romidepsin (Phase II trial of depsipeptide (NSC 630176) in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma)
AN10022	Development and validation of an integrated population pharmacokinetics model for romidepsin
AN10019	Integrated romidepsin exposure-QTc response population analysis
GPI-06-0005-QT	Romidepsin exposure-QTc response analysis, study GPI-06-0005

Evaluator's summary and conclusion on pharmacokinetics and pharmacodynamics

In these PK/PD studies romidepsin exhibited dose-proportional and linear PKs which did not change appreciably with repeated administration. Romidepsin PK was characterised by a three-compartment linear PK model. The mean AUC was 1549 ng.hr/ml, C_{max} was 377 ng/ml, half-life was 2.92 h and T_{max} was 4 h. Romidepsin exhibited moderate variability in its PK with the inter-subject variability in clearance (CL) and volume of central compartments (V_1) estimated to be 34% and 47% respectively.

In a population PK analysis, age, race, gender, mild to moderate or mild to severe renal impairment, and mild hepatic impairment had no effect on romidepsin PK. Study effect and weight were the two most significant predictors of romidepsin CL in the integrated population PK model. Weight accounted for approximately 2% of the variability in romidepsin CL and study effect explained 4% of the variability.

The potential of romidepsin to prolong the heart rate-corrected QT (QTc) interval was investigated in patients with advanced malignancies. The study revealed no concentration dependent effect of romidepsin on the duration of QTc interval, and both central tendency and categorical analyses showed no effect of dosing of romidepsin on QTc interval.

Dosage selection for the pivotal studies

The early clinical development of romidepsin included two Phase I dose escalation safety and tolerability studies (Study T-95-0022 and Study T-95-0077). Based on the maximum tolerated dose observed in Study T-95-0077 and the observed clinical activity in patients with T-cell lymphomas, the initial dose selected for the first Phase II efficacy and safety Study NCI 1312 was 17.8 mg/m² administered on Days 1 and 5 in a 21-day cycle. The dosing schedule was subsequently changed to 14mg/m² administered on Days 1, 8 and 15 in a 28 day cycle to improve tolerability. This dose was used in a pivotal study for CTCL (Study GPI-04-0001) initiated in 2005.

Based on encouraging results observed in Study NCI 1312 in heavily pre-treated and refractory patients with PTCL and the interim data available from patients with CTCL, a pivotal Phase II trial in patients with relapsed or refractory PTCL, Study GPI-06-0002, was planned and initiated in 2007.

Efficacy

Studies providing efficacy data

Key studies providing efficacy data are summarised in Table 4.

Table 4. Key clinical studies for romidepsin in T-cell Lymphomas

Study No.	Title	Indication	N
GPI-06-0002 Main study in MAA	A Phase II, Multicenter, Open-label Trial Evaluating the Activity and Tolerability of Romidepsin (depsipeptide, FK228) in Progressive or Relapsed Peripheral T-cell Lymphoma Following Prior Systemic Therapy	Relapsed refractory PTCL	131
NCI 1312 PTCL Supportive study in MAA	Phase II Study to Evaluate the Efficacy and Tolerability of Romidepsin in the Treatment of Patients with Cutaneous T-Cell Lymphoma (CTCL) or Peripheral T-cell Lymphoma (PTCL).	Relapsed refractory PTCL and CTCL	PTCL = 47 CTCL = 84
GPI-04 0001 Supportive safety data	A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T-Cell Lymphoma	Relapsed refractory CTCL	102

Study GPI-06-0002 (pivotal study)

The pivotal Study GPI-06-0002 was a Phase II, single arm, multicentre, open-label trial evaluating the activity and tolerability of romidepsin in progressive or relapsed PTCL following prior systemic therapy.

The sponsor indicated that the choice of a single arm design was based on several factors. Peripheral T-cell lymphoma is a rare and heterogeneous disease with many histological sub-types, making it difficult to accrue a sufficient number of homogenous patients to balance two separate treatment arms in a population with relapsed or refractory PTCL. At the time the study was initiated there were no other agents considered standard for second-line treatment of patients with PTCL. It was considered the alternative of using a placebo or best supportive care control was unethical in a disease with significant morbidity and mortality and in a patient population who had progressed despite prior systemic therapy.

Inclusion criteria for this study included male and female patients at least 18 years of age with histopathologically confirmed PTCL who had progressive disease following, or were refractory to, at least one prior systemic therapy.

Patients received romidepsin at a dose 14mg/m² IV over four hours on Days 1, 8 and 15 at each 28 Day cycle. Six cycles of treatment were planned and patients who developed progressive disease, significant toxicity or met other criteria for the study termination were to discontinue treatment. Responding patients had the option of continuing beyond six cycles if desired.

The primary endpoint for the study was the 'complete response rate' which is defined as both complete response (CR) and unconfirmed complete response (CRu) based on internationally recognised response criteria in patients with lymphoma (the International Workshop Criteria (IWC)).

The data reporting cut-off was 31st March 2010 but an updated analysis of the clinical data with a later cut-off date of the 31st October 2010 (or seven months after the initial data) was provided.

A summary of the main outcome data from the original and updated analyses is provided in Table 5.

Table 5. Original and Updated response rates and duration of response based on overall Independent Review Committee Review (Histopathologically Confirmed Population, N=130)

Efficacy Endpoint	Original Analysis ¹	Efficacy Update ²
Best Response Category, n (%) [95% CI]³		
Objective Disease Response (CR+CRu+PR)	34 (26.2) [18.8, 34.6] ³	33 (25.4) [18.2, 33.8] ³
Complete Response (CR+CRu)	17 (13.1) [7.8, 20.1] ³	19 (14.6) [9.0, 21.9] ³
Partial Response (PR)	17 (13.1) [7.8, 20.1] ³	14 (10.8) [6.0, 17.4] ³
Stable Disease (SD)	32 (24.6)	33 (25.4)
Progressive Disease (PD)	35 (26.9)	35 (26.9)
Not Evaluable ⁴	29 (22.3)	29 (22.3)
Duration of Response (Days)		
Patients with Objective Disease Response		
N	34	33
Median [95% CI]	353 [130, NE]	505 [353, NE]
Minimum, Maximum	1.0+ ⁶ , 801+	1.0+ ⁶ , 1035+
Censored Observations ⁵ , n (%)	26 (76.5)	25 (75.8)
Patients with Complete Response		
N	17	19
Median [95% CI]	NE [353, NE]	505 [353, NE]
Minimum, Maximum	1.0+ ⁶ , 801+	1.0+ ⁶ , 1035+
Censored Observations ⁵ , n (%)	16 (94.1)	17 (89.5)

Source for Updated Data: Section 6 Table 14.2.1.2, Table 14.2.7.2

Note: CI=confidence interval; NE=not estimated

1 Data through 31 March 2010 are included in this analysis.

2 Data through 31 October 2010 are included in this analysis.

3 Two-sided 95% confidence interval

4 Insufficient efficacy data to determine response due to early termination; included as non-responders in the analysis.

5 Censoring for the Overall IRC analysis was conducted based on the last clinical assessment date.

6 One patient elected to go to transplant following the first response assessment of CR.

Evaluator's conclusions on study GPI-06-0002 (pivotal study)

The data from the updated analyses indicate that the administration of romidepsin to the heavily pre-treated population of patients with PTCL is associated with a complete response rate of about 15% and an overall response rate of 25%. These data were consistent across the population and population sub-types, including histological sub-type, risk factors, and number and type and response to prior therapy. Responses were durable with a median duration of response of about 17 months for all responders. These data are therefore in line with evidence of worthwhile clinical benefit for patients who otherwise would have very limited therapeutic options available to them. The only area of uncertainty rests with the fact that this was a Phase II study without a comparator, although it is recognised that such selection would have been extremely difficult.

Study 1312 (supportive study)

The supportive study provided in this submission, NCI Study 1312, is a Phase II, open-label, multicentre, international study designed to evaluate the activity and tolerability of romidepsin in separate cohorts of patients with CTCL and PTCL. Initially the PTCL cohort in the study was restricted to patients with relapsed or refractory PTCL not otherwise specified (NOS) or primary cutaneous anaplastic large cell lymphoma (ALCL) who had not received more than two systemic cytotoxic chemotherapy regimens. Observed activity in the early phases of the trial led to amendment to include all sub-types of PTCL in patients who had previously received more than two cytotoxic therapies.

Inclusion criteria included male and female patients ≥ 18 years of age, all with measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2¹¹,

¹¹ The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0: Fully active, able to carry on all pre-disease performance without restriction

and life expectancy of at least 12 weeks. Central histopathological confirmation of PTCL was required.

Romidepsin was administered as a 4 h IV infusion on Days 1, 8 and 15 of a 28 Day cycle, with a starting dose of 14mg/m². It is noted that the first two patients in this study were treated with 18 mg/m² on Days 1 and 5 of a 21 Day cycle but the schedule was modified because of relatively poor tolerance.

A total of 45 patients were eligible for assessment of response to treatment. A summary of the main outcomes is shown below:

Table 6. Response to treatment (response evaluable population, NCI Study 1312)

Best Response Category	(N=45) n (%)
Objective Disease Response (CR+PR)	17 (37.8)
Complete Response (CR)	8 (17.8)
Partial Response (PR)	9 (20.0)
Stable Disease (SD)	5 (11.1)
Progressive Disease (PD)	18 (40.0)
Not Evaluable (NE)	5 (11.1)

Source: NCI Study 1312 manuscript

Evaluator's conclusions on study 1312

These supportive data support the evidence of efficacy for romidepsin in heavily previously treated patients with PTCL. Response rates observed, including the incidence of complete remission, are comparable to those from the pivotal trial.

Evaluator's conclusion on efficacy

Overall, the two studies, GPI-06-0002 and 1312, involving 175 patients, indicate definite activity of romidepsin in this patient population with at least a 15% complete remission rate and responses that are durable and clinically meaningful.

Safety

Studies providing safety data and exposure

This submission included safety data from a total of 891 patients who received at least one dose of romidepsin as monotherapy through to 30 September 2010 in clinical studies supported by Celgene or the US National Cancer Institute (NCI).

The clinical evaluator considered it most appropriate to concentrate on the safety data in relation to the two PTCL studies. Table 7 provides a summary of patient disposition and Table 8 provides a summary of exposure to romidepsin in these two studies.

-
- 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
 - 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
 - 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
 - 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
 - 5: Dead

Table 7. Patient Disposition, by Indication and Study: Patients with PTCL (N=178)

Patients:	Study		Total (N=178) n (%)
	GPI-06-0002 (N=131) n (%)	NCI 1312 (N=47) n (%)	
Treated	131 (100.0)	47 (100.0)	178 (100.0)
Treated in:			
Cycle 1	131 (100.0)	47 (100.0)	178 (100.0)
Cycle 2	98 (74.8)	38 (80.9)	136 (76.4)
Cycle 3	59 (45.0)	25 (53.2)	84 (47.2)
Cycle 4	50 (38.2)	22 (46.8)	72 (40.4)
Cycle 5	40 (30.5)	20 (42.6)	60 (33.7)
Cycle 6	35 (26.7)	16 (34.0)	51 (28.7)
Cycle >6	23 (17.6)	15 (31.9)	38 (21.3)
Treatment ongoing at cut-off date	18 (13.7)	5 (10.6)	23 (12.9)
Completed the study through Cycle 6			
Yes	33 ¹ (25.2)	15 (31.9)	48 (27.0)
No	97 (74.0)	32 (68.1)	129 (72.5)
If No, Reason for Discontinuation			
Progressive Disease	71 (54.2)	24 (51.1)	95 (53.4)
Adverse Event	19 (14.5)	2 (4.3)	21 (11.8)
Protocol Violation	1 (0.8)	0	1 (0.6)
Physician Decision	1 (0.8)	0	1 (0.6)
Withdrawal by Subject	3 (2.3)	0	3 (1.7)
Complicating Disease/Illness	0	2 (4.3)	2 (1.1)
Switched to Alternative Treatment	0	0	0
Death	0	2 (4.3)	2 (1.1)
Lost to Follow-Up	0	0	0
Other	2 (1.5)	2 (4.3)	4 (2.2)

Source: ISS PT_Table 1.

¹ One additional patient remained on treatment, but had only completed Cycle 5 as of data cut-off**Table 8. Exposure to romidepsin, by Study: Patients with PTCL (N=178)**

Parameter / Statistic	Study		Overall (N=178)
	GPI-06-0002 (N=131)	NCI 1312 (N=47)	
Number of Cycles Treated Overall			
N	131	47	178
Mean (±SD)	4.3 (4.72)	7.9 (10.67)	5.2 (6.97)
Median	2.0	3.0	2.0
Minimum, maximum	1, 31	1, 57	1, 57
Duration of Treatment (days)			
N	131	47	178
Mean (±SD)	105.3 (136.37)	245.8 (398.83)	142.4 (242.60)
Median	44.0	85.0	46.0
Minimum, maximum	1, 862	1, 1883	1, 1883
Total Dose of Romidepsin (mg)			
N	131	47	178
Mean (±SD)	276.3 (310.40)	491.4 (609.83)	333.1 (420.07)
Median	144.4	196.4	150.9
Minimum, maximum	26, 1616	25, 2391	25, 2391
Patients who received, n (%):			
No Dose Reduction	83 (63.4)	18 (38.3)	101 (56.7)
< 100% of expected dose ¹	41 (31.3)	21 (44.7)	62 (34.8)
< 80% of expected dose ¹	7 (5.3)	8 (17.0)	15 (8.4)
< 50% of expected dose ²	0	0	0

Source: ISS PT_Table 5.

¹ The expected dose over the course of the study was defined as the original dose multiplied by the number of doses given. To obtain the % expected dose received, the sum of the actual dose was calculated, then divided by the expected dose (and multiplied by 100).

Analyses of adverse events (AEs) during the two studies were performed on treatment emergent AEs (TEAEs), defined as those events that start during romidepsin

administration or through 30 days after the last dose. All AEs that are study drug related and all events present at baseline that worsened in intensity were subsequently considered drug related. Assessment of grading of toxicities was determined by NCI toxicity criteria. Methodological differences between the pivotal study and NCI Study 1312 included differences in the visit and evaluation schedules, AE reporting procedures, and documentation of treatment for AEs. Also there were differences in the patient characteristics in each study population with patients in NCI Study 1312 having more advanced disease and receiving more prior lines of therapy.

An overall summary of the categories of AEs reported in the two studies is shown in Table 9. As indicated, approximately 97% of patients experienced at least one TEAE of which 71% were at least Grade III and 27% at least Grade IV in intensity. Fifty-one per cent of patients experienced at least one serious AE (SAE) and 8% of patients had an AE that resulted in death. Overall, 20% of patients discontinued the study drug because of an AE.

Table 9. Summary of Treatment-emergent Adverse Events, by Study: Patients with PTCL (N=178)

	Study		
	GPI-06-0002 (N=131) n (%)	NCI 1312 (N=47) n (%)	Total (N=178) n (%)
Patients with at least one:			
Treatment-emergent AE (TEAE)	126 (96.2)	47 (100.0)	173 (97.2)
Treatment-related TEAE ¹	120 (91.6)	47 (100.0)	167 (93.8)
≥Grade 3 TEAE ²	86 (65.6)	40 (85.1)	126 (70.8)
≥Grade 4 TEAE ²	26 (19.8)	22 (46.8)	48 (27.0)
Serious TEAE	60 (45.8)	30 (63.8)	90 (50.6)
TEAE leading to study drug discontinuation	22 (16.8)	13 (27.7)	35 (19.7)
TEAE resulting in death	7 (5.3)	8 (17.0)	15 (8.4)

Source: ISS PT, Table 7.1.

¹ Treatment-related adverse events are those indicated by the Investigator as having a possible, probably, or definite/certain/likely relationship to study drug.

² Includes events with missing toxicity assessment; a toxicity assessment was missing for a total of 2 events, both in Study GPI-06-0002 (alanine aminotransferase increased in Patient 0109-0137 and pyrexia in Patient 0404-0012).

Post marketing safety data

Romidepsin was approved in the US on the 5th November 2009 for the treatment of patients with CTCL who had received at least one prior systemic therapy. Romidepsin is not currently marketed outside the U.S. Post-marketing data for romidepsin are based on four periodic adverse experience reports submitted to the FDA through 30th October 2010. A total of 652-978 treatment cycles have been given in 6-8 vials per cycle. The most common AEs reported were fatigue in four patients, sudden death in four patients and disease progression, asthenia, EBV virus infection, ECG T-wave inversion, laboratory test abnormalities, decreased platelet counts, decreased appetite and dysgeusia, all in two patients each.

Evaluator's conclusion on safety

The safety data from the two studies has generally outlined AEs that are consistent with those observed in nonclinical and previous clinical studies. It is to be noted that the toxicities encountered are generally well recognised in conjunction with various cancer chemotherapies, including gastrointestinal disturbances, haematologic toxicities, asthenic conditions and infections. These can be generally well managed in most circumstances and there is no data from these two studies to suggest that there would be greater difficulties for oncologists with this agent.

First round benefit-risk assessment

First round assessment of benefits

The pivotal Study GPI-06-0002, a Phase II trial evaluating romidepsin in patients with previously treated PTCL, has demonstrated in 130 histologically confirmed patients a complete response rate of 13.1% and an overall objective response rate of 26.2%, based on the original cut-off date of March 2010. In the updated efficacy analysis of October 2010, the complete response rate was 14.6% and the overall objective response rate was 25.4%. In this heavily pre-treated patient population including a significant proportion of patients who had received prior autologous stem cell infusions this is quite an impressive response. The responses appear to be durable with an overall median duration of response of 12 months and median duration of complete response not yet reached, based on the original cut-off of March 2010. In the updated efficacy analysis, the overall median duration of response and the median duration of complete response were both 17 months.

Various sub-group analyses have confirmed this response data. With respect to the issue of this being a Phase II study, it is noted that in general terms undertaking a Phase III trial would be more appropriate, but recognising the relatively uncommon nature of PTCL and most particularly its considerable variability in histological sub-types as well as responsiveness to therapy, such a Phase III trial would have difficulties to undertake. With regards to decisions regarding complete response as the primary efficacy endpoint it is generally recognised that in Phase II trials complete response is a good indicator of likely benefit for therapy translating to improved progression free survival and overall survival.

The supportive Study NCI 1312 in a patient population of 45 patients with histologically confirmed PTCL demonstrated a complete response rate of 17.8% and an objective disease response rate of 37.8%. There was a median overall response duration of 9 months and 17 months for complete response. Again this data tends to support and confirm that from the pivotal trial.

Accordingly the evaluator considered that there is every indication that romidepsin has worthwhile clinical activity in patients with previously treated PTCL that may well translate to further benefit as potential first-line therapy and in combination with other approaches. Further studies will determine this.

First round assessment of risks

The safety profile observed in the two studies of patients with PTCL evaluated in this submission was consistent with anticipated events in a patient population with advanced, previously treated PTCL who have received prior chemotherapy. The safety profile was also consistent with the effects observed in nonclinical and previous clinical studies of romidepsin. The most common AEs were functional gastrointestinal disturbances, haematologic toxicities, asthenic conditions and infections. While the incidence of these AEs was common they were generally mild to moderate in severity with severe AEs being relatively uncommon. It is noted however that there were 10 TEAEs resulting in death, although 5 of the deaths were considered directly due to disease progression while for the remaining 5 the primary cause of death was an infection or an event that occurred in the setting of infection. All but one of these deaths was considered by the investigator unrelated to study drug. In general the AE profile is one which is familiar to oncologists managing patients on chemotherapy and recognises the requirements for appropriate prophylactic and early interventional management. The evaluator does not consider that the profile exhibited from these studies represents excessive risk for patients with advanced stage PTCL who otherwise would have a very limited duration of survival.

First round assessment of benefit-risk balance

As has been indicated above, the pivotal study involving 130 patients has established definite efficacy for romidepsin in the management of patients with relapsed and refractory PTCL who have previously been heavily treated, with a complete response rate of 13.1% and an overall response rate of 26.2%. These responses were durable and various analyses including sub-group analyses have supported the legitimacy of the findings. Data from the supportive Study NCI 1312 were also indicative of complete response rate of 17.8% and overall response rate of 37.8%.

The toxicity profile is generally consistent with that to be expected with various chemotherapeutic agents and is generally associated with well-known forms of toxicities including gastrointestinal, haematological and asthenia. These have appeared to be generally manageable and well within the province of oncologists areas of expertise. Accordingly the evaluator considers the benefit-risk balance favourable.

List of questions

None

Recommendation regarding authorisation

The evaluator considers that on balance and in view of the discussion indicated above there is evidence of definite efficacy for romidepsin in the treatment of advanced stage relapsed and refractory PTCL. Despite the fact that the studies involved were Phase II in nature without a direct comparator, the evaluator considers that the overall evidence of benefit versus the relative risks involved would support approval for marketing of this agent.

It is also worth commenting that approval for romidepsin in the management of patients with advanced stage refractory and relapsed PTCL has been given by the US FDA.

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan (EU-RMP Version 3.0 (dated 05/05/2012, DLP 31/10/2010), and Australian Specific Annex Version 1.0 (dated 08/06/2012)) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 10):

Table 10. Important identified and potential risks and missing information.

Important identified risks:	Haematological toxicity Infections Electrocardiogram changes Gastrointestinal disorders Tumour lysis syndrome
Important potential risks:	Reproductive toxicity Venous thromboembolism Hypersensitivity reactions DNA virus reactivation Interaction with drugs that inhibit or induce cytochrome CYP P450 3A4 enzymes Interaction with drugs that inhibit the ABCB1 (P-gp) drug transport systems Interaction with warfarin or warfarin derivatives Interaction with Oestrogen-containing contraceptives
Important missing information:	Risk in hepatic impairment Risk in patients with congestive heart failure NYHA Class II to IV or LVEF <50% Risk in renal impairment Risk in pregnant or lactating women Risk in children Risks in off label use for CTCL in the EU

OPR reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, this is considered acceptable.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some risks: clinical trials are planned to further study potential drug interactions and the risk in patients with impaired hepatic function, and a drug utilisation study in Europe is planned to study the risks in off-label use.

Risk minimisation activities

No additional risk minimisation activities are proposed for Istodax.

Summary of first round recommendations

The OPR provides these recommendations in the context that the submitted RMP (EU-RMP Version 3.0 (dated 05/05/2012, DLP 31/10/2010), and Australian Specific Annex Version 1.0 (dated 08/06/2012)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received:

Further safety considerations

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical

evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor was asked to provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to pharmacovigilance activities

1. The sponsor should provide an estimated planned date of submission of final data for the planned drug utilisation study as soon as it becomes available.

Recommendations in regard to risk minimisation activities

1. In regard to the proposed routine risk minimisation activities, several revisions to the draft PI were recommended. Details of these recommendations are beyond the scope of the AusPAR.

Second round evaluation

Recommendations in regard to pharmacovigilance activities

The sponsor advised that *'the proposed drug utilisation study mentioned in the EU RMP was planned for the EU region only. As the EU MAA has now received a negative opinion, Celgene does not plan to conduct this study.'* This is acceptable.

Recommendations in regard to risk minimisation activities

The sponsor provided acceptable responses to many of the recommended revisions to the PI. Outstanding matters regarding the PI were drawn to the attention of the Delegate for further discussion with the sponsor.

Responses to other recommendations were satisfactory.

Conclusion and recommendation

The RMP evaluator considered that the sponsor's response to the above recommendations adequately addressed all of the issues identified in the RMP evaluation report, except for some of the recommended revisions to the PI.

In the event of approval, the following should be considered:

- Implement EU-RMP Version 3.0 (dated 05/05/2012, DLP 31/10/2010), and Australian Specific Annex Version 1.0 (dated 08/06/2012), and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Celgene Australia Pty Ltd have applied to register romidepsin (tradenname: Istodax) powder for IV infusion. The sponsor's proposed indication is: *Istodax is indicated for the treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least one prior therapy.* The proposed dose is 14 mg/m² over a 4 h period on Days 1, 8 and 15 of

a 28 Day cycle. Cycles may be repeated while the patient benefits from and tolerates therapy.

Targets and mechanism of action

Romidepsin is a cyclic bipeptide produced by traditional fermentation as a secondary metabolite by a strain of *Chromobacterium violaceum*, a naturally occurring soil bacterium that has been mutated to enhance production of romidepsin.

Romidepsin is a histone deacetylase inhibitor (HDACi).¹² Others are vorinostat (registered in Australia for cutaneous manifestations in patients with CTCL after prior systemic therapies, and FDA-approved for third line use in CTCL), panobinostat and belinostat.

The nonclinical evaluation report notes that a screen of 62 receptors and ion channels found an interaction between romidepsin and the oestrogen and NK₂ receptors at romidepsin levels higher than typically seen in clinical studies. NK₂ receptors have been implicated in regulation of haematopoiesis.¹³

Peripheral T-cell lymphoma (PTCL)

Peripheral T-cell lymphoma comprises 7-15% of Non-Hodgkin's Lymphomas; "peripheral" refers to maturity of the neoplastic T cell (it is post-thymic, peripheral to the thymus). Outcome is generally poor but exceptions exist (for example, patients with anaplastic lymphoma kinase (ALK) positive ALCL). There are many subtypes within the PTCL grouping.

There are currently no TGA-registered treatments for PTCL. There is no 'standard of care' treatment but a commonly cited first-line treatment is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Stem cell transplant (SCT) is curative in a small subgroup. PTCL patients are often managed by enrolment into clinical trials of novel agents.

Regulation

Romidepsin has Orphan status for treatment of patients with PTCL (or cutaneous TCL) who have received at least one prior systemic therapy.

Overseas status

USA: Romidepsin has been approved by the FDA for the treatment of patients with relapsed / refractory PTCL or relapsed / refractory CTCL.

EU: CHMP has confirmed a negative opinion about a similar application for romidepsin. The sponsor writes: *The CHMP acknowledged the high level of activity of romidepsin, the acceptable safety profile and the unmet medical need of relapsed / refractory PTCL; however,*

¹² Histones are the main proteins of chromatin; histone deacetylases remove acetyl groups (e.g. from histone's acetyl lysine amino acids). Non-histone proteins are also targeted by histone deacetylases. HDAC inhibitors induce hyper-acetylation. Professor H. Miles Prince (an investigator in the romidepsin studies), writes:

- The balance between acetylation (mediated by histone acetylases (HATs)) and deacetylation (mediated by HDACs) controls gene transcription. Deacetylation of histone proteins by HDACs promotes closed chromatin and inhibition of gene transcription.
- For HDAC inhibitors, acetylation of non-histone proteins is likely also critically important.
- HDACi have wide-ranging effects on malignant cells including inhibition of cell differentiation, cell cycle growth arrest, inhibition of angiogenesis, apoptosis, autophagy and immune modulation.
- 18 HDAC enzymes are divided into four classes. HDACi may have broad anti-HDAC activity (e.g. vorinostat, panobinostat and belinostat) or more specific class 1 activity such as romidepsin.

¹³ Klassert *et al.* Tachykinins and neurokinin receptors in bone marrow function: neural-hematopoietic link. *J Receptor Ligand Channel Res.* 2010 April 1; 2010 (3): 51-61

the CHMP's main concern from the initial opinion remained in that it could not conclude on the clinical benefit-risk ratio of Istodax due the absence of a comparator in the pivotal Phase II study (GPI-06-002).

Quality

There are no chemistry and quality control objections to registration, pending resolution of two issues:

- A proposed drug substance limit for an unknown impurity requires toxicological qualification or reduction. Attempts to identify the impurity should be described.
- There should be a reduced finished product limit for residual *tert*-butyl alcohol and provision of revised finished product specifications.

Nonclinical

The nonclinical evaluator considered romidepsin approvable "only if the adverse events are clinically manageable".

tert-Butyl alcohol is a residual solvent. The nonclinical evaluator was concerned about the safety of TBA. For example, in a short-term repeat dose study with TBA, transitional cell hyperplasia and inflammation of the renal pelvis and urinary bladder were seen at all doses, including the lowest. The lowest dose tested was 18 fold above maximum clinical exposure. The sponsor argues that hyperplastic changes do not indicate a risk of cancer in the case of romidepsin given to humans.

Clinical

Overview of data

Efficacy and safety of romidepsin in relapsed or refractory PTCL have been evaluated in two clinical trials, neither of which was controlled:

- Study GPI-06-0002: a Phase II study in 131 relapsed or refractory PTCL patients at 49 study centres. This trial was described by the sponsor as pivotal and also "the largest clinical trial conducted to date in patients with this rare disease". This study has been published.¹⁴
- NCI Study 1312: a Phase II study in 47 heavily pre-treated patients (CTCL patients were studied as well). This trial was described as supportive.

The submission is based on a data cut-off of March 2010 for GPI-06-0002, giving median follow-up of 8.2 months and maximum duration of treatment of 2.4 years. NCI Study 1312 included maximum duration of treatment of 5 years.

Eight studies contributed to the pharmacological characterisation of romidepsin.

Pharmacokinetics (PK)

Clinical PK characterisation was not extensive.

A large volume of distribution was inferred but not well quantified. There was very low distribution to the CNS, based on studies in dogs.

¹⁴ Coiffer, Pro, Prince *et al.* Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 2012 Feb 20; 30 (6): 631-636.

In Study T-95-0077 (dose-ranging; various cancers), systemic exposure was proportional to dose over the range studied, 1-24.9 mg/m². In those with more than one evaluable profile, PK did not change much with repeat dosing. In non-compartmental analysis of data from Study 1312, mean AUC was 1549 ng.hr/mL, mean C_{max} was 377 ng/mL, mean t_½ was 2.9 h and mean T_{max} was 4 h.

Metabolism was via CYP3A4 and via non-enzymatic pathways. No one metabolite predominated. There was a lack of *in vivo* studies in animals or humans.

The supportive efficacy Study NCI 1312 had a PK component. Clearance was variable across patients but the studied group was heterogeneous.

Study AN10022 aimed to develop a population PK model for romidepsin. Data from six romidepsin studies were used; some studies used intense sampling, others sparse. The analysis suggested that weight was a predictor of romidepsin clearance; weight is correlated with body surface area (BSA), and romidepsin is dosed according to BSA.

There was no relationship found between various degrees of renal function (end stage renal failure (ESRF) was not assessed) and romidepsin clearance.

Hepatic impairment did not significantly predict variation in clearance, based on analysis of 120 patients with normal function, 15 with mild impairment and 2 with moderate impairment, but the sponsor plans a dedicated study in this area.

Drug interactions: *In vitro* studies suggested significant inhibition of romidepsin metabolism via CYP3A4 by ketoconazole; a formal study is planned (as is one with rifampin). The nonclinical evaluator concluded that romidepsin was unlikely to cause significant CYP inhibition and was likely to cause only very minor CYP induction.

The nonclinical evaluator noted that in a colon carcinoma cell line, romidepsin induced drug resistance via up-regulation of P-gp. Romidepsin is a substrate of P-gp. There was *in vitro* evidence of cross-resistance to paclitaxel and doxorubicin (P-gp substrates). Romidepsin does not inhibit P-gp but induction of P-gp may occur. PTCLs have been reported to overexpress MDRP1 / P-gp (for example, see Mahadevan *et al.*, *Cancer* 2013; 119:371-379).

Also with regard to drug interactions, the sponsor states: Analyses comparing the incidence of AEs by concomitant medication use in the Study GPI-06-0002 (QT prolonging drugs, moderate to strong CYP 3A4 inhibitors, steroids, narcotics, oral hypoglycemics, anti-emetics and neuroleptics) did not reveal any clear, clinically meaningful findings that suggested any change in therapeutic approach on the basis of concomitant use of any of these types of medications.

Other findings of note included that in Study T-95-0022 (dose-ranging; various cancers) showing that the maximum tolerated dose was 10 mg/m² without anti-emetics and 13.3 mg/m² with anti-emetics.

Efficacy

Study GPI-06-0002 (pivotal)

This was an open-label, uncontrolled, multi-centre study of romidepsin used as 2nd or subsequent-line therapy in 131 patients with PTCL (including 15/131 from Australia). The data cut-off used in the clinical study report (CSR) was 31 March 2010.

Patients ≥18 years with histopathologically confirmed PTCL who had progressive disease following, or were refractory to, at least one prior systemic therapy were included. Patients with untransformed mycosis fungoides or with Sezary Syndrome were excluded; other exclusions are mentioned in the CER (see Attachment 2 of this AusPAR). One

exclusion was “known significant cardiac abnormalities” (for example, arrhythmias requiring medication).

The intent to treat (ITT) population was 130 (one patient did not have a confirmed diagnosis). The baseline characteristics of the group are set out in the attached CER. Notably, PTCL NOS was the predominant subtype, with angioimmunoblastic T-cell lymphoma (AITL) then ALK-negative ALCL next in line. Other subtypes were represented by 6 or fewer subjects. Median number of prior treatments was 2 (range, 1-8). The evaluator notes that the commonest prior therapy was CHOP. Median time since last systemic therapy was 2.1 months, indicative of rapid progression for many patients. These data indicate a patient population with a generally poor prognosis.

Intervention: Patients received romidepsin 14 mg/m² IV over 4 h on Days 1, 8 and 15 within each 28 Day cycle. Six cycles were planned. Responding patients had the option of further cycles of romidepsin.

131 patients received at least one dose of romidepsin in this study. 59 patients (45%) received 3 or more cycles, including 35/131 (27%) who received 6 or more cycles. Of these 35, 15 patients received 9 or more cycles. 80% of patients within each cycle received two or three doses. Mean and median durations of treatment were 105 and 44 days, respectively; the maximum was 2.4 yrs.

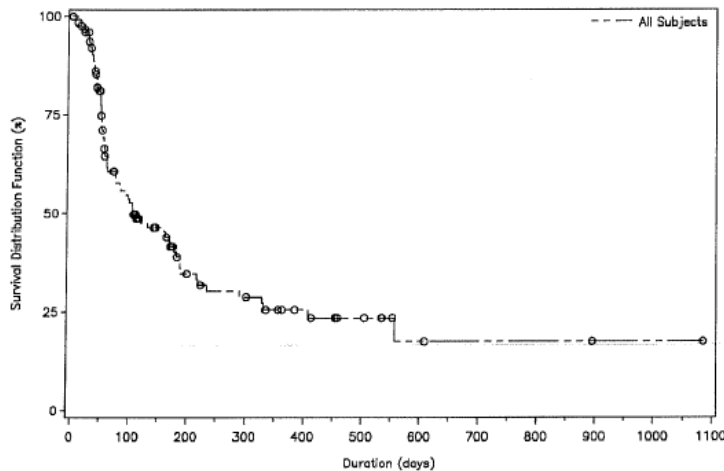
Efficacy evaluation: The study’s primary endpoint was complete response rate (including unconfirmed complete response) based on independent review committee (IRC) assessment. Duration of response was the key secondary endpoint.

Objective response rate: Based on IRC assessment, complete response was seen in 13.1%; partial response was seen in 13.1%, making the objective response rate 26.2%. There was disparity in the fraction classified as having progressive disease by IRC versus investigators’ assessment (26.9% versus 45.4% respectively). Time to response was relatively short, with a median of 2 cycles before objective response (median of 4 cycles for complete response). Complete response was not concentrated in any one PTCL subtype, or over-represented in subjects with 1-2 prior therapies. Nine complete responders had improved functional performance (measured by a shift in ECOG status) at some time on study.

Duration of response: Objective responses were often durable. For example, amongst the 17 patients with a complete response (complete response + complete response unconfirmed), median duration of that response was not reached (that is, at least half of subjects had maintained their response); based on investigator’s assessment, median duration of complete response was 429 days. Using the initial cut-off date, 16/17 complete responders had not relapsed and had maintained complete response for at least 2 months; median follow-up was 8.2 months.

Progression-free survival: Median progression-free survival was 107 days (IRC assessment), or 77 days based on investigator assessment. The survival curve is at Figure 2. A reasonable minority of subjects were progression-free at the data-cut-off.

Figure 2. Kaplan-Meier curve of PFS based on overall IRC review (ITT; updated cut-off)



Overall survival: Median overall survival was 11.3 months from start of romidepsin; median overall survival was not reached in complete responders and was 550 days in partial responders.

Efficacy update. In an update using a 31 October 2010 cut-off, best response was complete for 19/130 subjects and partial for 14/130 (compared with 17/130 and 17/130 respectively at the initial cut-off). Median duration of complete response was 505 days at this cut-off; maximum duration of complete response was 1035+ days. Nine of 19 complete responders remained on treatment (and it is known they also remained on treatment to at least 14 March 2011). Of the 10 complete responders off treatment, only 1/10 had progression as of the last observation.

- 13/19 subjects (68%; or 10% of the whole population) had a duration of complete response >6 months.
- 7/19 subjects (37%; or 5.4% of the whole ITT population) had a duration of complete response >12 months.

The efficacy update did not raise any further concern about robustness of initial results.

Study NCI 1312 (supportive)

This open, uncontrolled, Phase II study examined mainly relapsed or refractory PTCL patients. It was started >6 years prior to the pivotal study. 46/47 patients had PTCL; 1 had CTCL. Median number of prior treatments was 3 (range 1-11). 45/47 patients were eligible for assessment of response. 8/45 (17.8%) had a complete response; median duration of complete response was 29.7 months. 5/8 complete responders (4/45 or 11.1% of the assessed patients) had a complete response of ≥ 12 months (12, 23+, 17, 49+ and 74 months). These data are broadly consistent with the efficacy data from the pivotal study.

Historical controls

The sponsor used the following historical / external controls for the purpose of “descriptive comparison”. Romidepsin’s ‘investigator assessments’ were used for this purpose since the external studies also relied on investigator assessment. Safety was not compared.

- “GELA” (Groupe d’Etude des Lymphomes de l’Adulte) studies (4 Phase II studies in patients with previously untreated PTCL; the sponsor reviewed medical records of all enrolled patients to obtain information about subsequent lines of therapy)

- MSKCC (Memorial Sloan Kettering Cancer Center) PTCL patients
- UNMC (University of Nebraska Medical Center) PTCL patients

From these three sources, 205 patients with relapsed or refractory PTCL were included (others were excluded if they would not have been eligible for enrolment in Study GPI-06-0002). Table 11 indicates that romidepsin outcomes were similar to historical outcomes for 3rd line therapy, and better for 4th line therapy (subsequent lines were not analysed). For 2nd line therapy, responses favoured historical outcomes; the sponsor states: *this difference is not unexpected given that 82% of patients in the External Control dataset received combination chemotherapy or underwent high-dose therapy with bone marrow transplant.*

Safety was compared with regimens used in treatment of Non-Hodgkin's lymphoma (NHL) but these comparisons are of even less direct relevance and equally prone to bias.

Table 11. Comparison of response to any therapy administered for PTCL in the external control dataset and best response to Romidepsin in Study GPI-06-0002 by line of therapy.

Response to Therapy	External Controls			GPI-06-0002 (N=130)
	Cooperative Group (N=116)	Hospital Group (N=89)	Total External Control (N=205)	
2nd Line, n	116	89	205	40
ORR, n (%)	51 (44.0)	46 (51.7)	97 (47.3)	13 (32.5)
[95% CI]	[34.8, 53.5]	[40.8, 62.4]	[40.3, 54.4]	[18.6, 49.1]
CR, n (%)	41 (35.3)	25 (28.1)	66 (32.2)	7 (17.5)
[95% CI]	[26.7, 44.8]	[19.1, 38.6]	[25.9, 39.1]	[7.3, 32.8]
PD/SD ^a , n (%)	65 (56.0)	43 (48.3)	108 (52.7)	27 (67.5)
[95% CI]	[46.5, 65.2]	[37.6, 59.2]	[45.6, 59.7]	[50.9, 81.4]
3rd Line, n	56	40	96	48
ORR, n (%)	13 (23.2)	13 (32.5)	26 (27.1)	14 (29.2)
[95% CI]	[13.0, 36.4]	[18.6, 49.1]	[18.5, 37.1]	[17.0, 44.1]
CR, n (%)	7 (12.5)	7 (17.5)	14 (14.6)	7 (14.6)
[95% CI]	[5.2, 24.1]	[7.3, 32.8]	[8.2, 23.3]	[6.1, 27.8]
PD/SD ^a , n (%)	43 (76.8)	27 (67.5)	70 (72.9)	34 (70.8)
[95% CI]	[63.6, 87.0]	[50.9, 81.4]	[62.9, 81.5]	[55.9, 83.0]
4th Line, n	17	21	38	15
ORR, n (%)	1 (5.9)	8 (38.1)	9 (23.7)	4 (26.7)
[95% CI]	[0.1, 28.7]	[18.1, 61.6]	[11.4, 40.2]	[7.8, 55.1]
CR, n (%)	1 (5.9)	2 (9.5)	3 (7.9)	3 (20.0)
[95% CI]	[0.1, 28.7]	[1.2, 30.4]	[1.7, 21.4]	[4.3, 48.1]
PD/SD ^a , n (%)	16 (94.1)	13 (61.9)	29 (76.3)	11 (73.3)
[95% CI]	[71.3, 99.9]	[38.4, 81.9]	[59.8, 88.6]	[44.9, 92.2]

Source: Section 6, Table 14.2.1

a Includes patients with response of not evaluable/assessable

Cross-study comparison with pralatrexate

Romidepsin outcomes were also compared to pralatrexate outcomes in PROPEL (the pivotal study performed for pralatrexate) in which a similar patient population was studied. The sponsor concluded that romidepsin achieved higher complete response rates and longer duration of response than did pralatrexate and that romidepsin has a more favourable safety profile (for example, no mucositis; less hepatotoxicity; less skin toxicity; perhaps less haematological toxicity).

Safety

Exposure

Safety was evaluated in 891 patients who received ≥ 1 dose of romidepsin, up to October 2010 in Celgene trials (n=327) and NCI trials (n=564). The NCI figure in particular included patients with non-haematological malignancies. The two efficacy studies of PTCL patients contributed 178 patients (according to the CER, one of these patients in NCI 1312

did not have confirmed PTCL). In PTCL patients, the median number of cycles was 2 and the median treatment duration was 1.5 months. Mean values were higher (some patients received many cycles). Across the two PTCL studies, AEs can be summarised as in Table 9 above. Table 12 sets out exposure across cycles 1-6 in Study GPI-06-0002 and also shows the extent of dose reductions and delays across these cycles.

Table 12. Summary of number of doses administered, missed doses and dose reductions by Cycle through Cycle 6 (as Treated Population, N=131)

Number of Patients:	C1	C2	C3	C4	C5	C6
Receiving at Least: ¹						
1 Dose	131 (100.0)	98 (100.0)	59 (100.0)	50 (100.0)	40 (100.0)	35 (100.0)
2 Doses	126 (96.2)	81 (82.7)	54 (91.5)	46 (92.0)	37 (92.5)	33 (94.3)
3 Doses	90 (68.7)	67 (68.4)	47 (79.7)	38 (76.0)	35 (87.5)	28 (80.0)
With Dose Delay ^{1,2}	14 (10.7)	19 (19.4)	9 (15.3)	4 (8.0)	5 (12.5)	3 (8.6)
With Dose Reductions ^{1,2}	3 (2.3)	9 (9.2)	4 (6.8)	1 (2.0)	1 (2.5)	1 (2.9)

Source: Study GPI-06-0002, Table 14.4.3.

¹ Percent based on the number of patients on treatment within that cycle.

² As reported on the dosing CRF.

There has been some post-marketing experience in the USA: the sponsor notes 652-978 treatment cycles have been given (5867 vials have been sold), which is quite limited market experience.

Deaths

Three patients (in the PTCL set of 178) died due to AEs possibly or probably related to romidepsin. In 2/3, infection was present. Eight others died after infection. Key toxicities included:

- Gastrointestinal effects

AEs involving the gastrointestinal tract, including nausea, vomiting, diarrhoea and constipation, were very common. Severe (Grade ≥ 3) nausea and vomiting were reported in 3% and 6% respectively. Preventive anti-emetic support was the norm (85%).

- Haematological effects

Haematological toxicity was common. In the pivotal study, severe thrombocytopenia was reported in 24%; neutropenia in 20%; anaemia in 10%; and lymphopenia in 3%. Frequencies were higher in the supportive study. These AEs often caused dose interruption and, less often, drug discontinuation. There was no evidence of cumulative toxicity, though subjects were still reporting these AEs after 6 cycles. Thrombocytopenia was more frequent in those with >1 prior therapy, perhaps due to reduced bone marrow reserve. Severe neutropenia was more common with prior use of monoclonal antibodies. Haematological toxicity and infection were more apparent in those with known bone marrow involvement.

- Infection was a commonly reported class of AE, and Grade ≥ 3 infection was reported in 35/178 subjects. There were 8 cases of febrile neutropenia. There were 5 cases of severe pneumonia or sepsis in patients with neutropenia.
- Bleeding was reported as an AE on 23 occasions. There were 4 cases of bleeding related to treatment and with concomitant low platelets.

The clinical evaluator states that there was a relatively low incidence of transfusions and use of growth factors in the pivotal study; use was not recorded in NCI 1312.

The nonclinical evaluator canvassed the possibility of irreversible haematopoietic effects but this was based on limited data. Also, thrombocytopenia and neutropenia observed in

clinical trials were reversible, according to the sponsor “resolving shortly after discontinuation of therapy”.

The sponsor links thrombocytopenia to an effect on megakaryocyte maturation (via inhibition of the transcription factor GATA expression) rather than any direct cytotoxic effect; the sponsor also states that “it has been hypothesised that thrombocytopenia associated with HDAC inhibitors is cytokine-mediated” however the two positions are not incompatible.

- Infection

Infection was common. Pneumonia and sepsis were prominent. 12% needed dose suspension or reduction due to infection and 3% discontinued (out of 178 patients). Pyrexia and febrile neutropenia were also prominent treatment-related SAEs.

The sponsor found no link between severe neutropenia or lymphopenia and infection but the sponsor found links between prior monoclonal antibody use and infection, and between prior monoclonal antibody use and severe neutropenia (so a link might in fact exist between severe neutropenia and infection, as might be suspected on biological grounds).

Epstein-Barr virus (EBV) reactivation has been reported in clinical trials and in the post-marketing setting.

- Laboratory findings

Differences between Study GPI-06-0002 and NCI 1312 in rates of laboratory abnormalities are ascribed to methodological differences (essentially more intensive monitoring in 45% of NCI 1312 patients). Based on NCI 1312 (which might have studied more intensively pre-treated subjects), grade ≥ 3 events occurred as follows: hypocalcaemia in 14.9% (unclear if levels were corrected for albumin), hypoalbuminaemia in 10.6%; AST elevated in 12.8%; ALT elevated in 14.9%; and hyperglycaemia in 8.5%.

QT prolongation (ascribed to romidepsin) caused treatment discontinuation in 2/178 PTCL subjects, despite the negative pharmacodynamic study findings. In two patients, ventricular arrhythmias were reported as serious treatment-related AEs. Another ECG finding was decreased T wave amplitude.

- Liver abnormalities

Treatment-emergent increases in AST and ALT were slightly more common at Cycles 5-6 and more frequent again after Cycle 6, suggesting a dose-related risk of liver injury. This pattern was less evident for hyperbilirubinaemia, however after Cycle 6 the frequency of hyperbilirubinaemia was increased relative to Cycles 1-6. Hyperbilirubinaemia was reported as an AE in 1/131 patients (Study GPI-06-0002) but in 14/47 (30%) in Study NCI 1312, illustrating the different safety assessment methods used. Autoimmune haemolytic anaemia was also reported at least twice but the sponsor did not discuss whether haemolysis might account for the high frequency of hyperbilirubinaemia (and contribute to anaemia).

Nine patients (5%) had ‘serious’ LFT abnormalities but in 7/9 the change resolved despite continuing treatment. In 5 patients, transaminase elevations >3 times the upper limit of normal were accompanied by elevated bilirubin >2 times the upper limit of normal but in each case there was a reasonable non-drug explanation.

- Cardiovascular effects

Patients with a significant cardiac history, a baseline QTc interval >450 msec, a history of congenital long QT syndrome, ventricular tachycardia, torsade de pointes (TdP), ventricular fibrillation, bradycardia <50 beats per min (bpm), congestive heart failure

≥Grade 3 New York Heart Association (NYHA criteria), or myocardial infarction within 6 months before entry were excluded from clinical studies.

The sponsor states that ECG abnormalities such as ST- and T- wave flattening and ST segment depression may be a class effect of HDAC inhibitors; these changes were observed in more than half of T cell lymphoma patients treated with romidepsin. The sponsor states that there was no association with functional impairment or evidence of myocardial damage, even in patients treated for >6 months.

Study GPI-06-0005-QT examined romidepsin's effect on the ECG QT interval, and examined the exposure (C_{max})-response relationship. No effect on QT was seen; this is at odds with nonclinical studies of cardiovascular safety where modest effects were seen. The sponsor's own conclusion is that romidepsin has a modest QT prolonging effect (5 msec) and that some of this may be attributable to use of anti-emetics (however it was recommended QT-prolonging anti-emetics not be used).

In clinical studies, a few patients reported QT prolongation (without syncope or cardiac AEs). In the post-marketing setting, there have been 4 reports of sudden death (<1000 patients have been exposed). A clinical study amendment stipulated use of supplemental potassium and magnesium for patients with low levels, before administering romidepsin, to lower the risk of QT prolongation.

Hypotension was relatively common. It was usually low-grade but more severe cases were observed in NCI 1312 (3 patients discontinued because of this AE). At least 4 patients experienced hypotension on a dosing day. Nonclinical studies were inconclusive but suggested possible direct cardiomyocyte toxicity.

An effect of romidepsin on heart rate (HR) was noted. Romidepsin was associated with a delayed concentration-dependent increase in HR, with maximum mean increase in HR of 20 bpm at 6 h, after a 4 h infusion. Tachycardia was reported in 13/178 PTCL patients (7.3%); the separate term sinus tachycardia was also reported in 4 patients. Potentially, tachycardia could be secondary to drug-induced hypotension.

Venous thromboembolism was reported in 8 patients across studies; 2 patients discontinued study drug because of this AE.

- Fertility and teratogenicity

Romidepsin is likely to compromise fertility and be teratogenic, based on general toxicity studies. Reversibility of changes (for example, testicular lesions in mice) was not seen 4 weeks after the last dose of romidepsin. Fetal toxicity was seen at very low exposure levels and the non-clinical evaluator recommended that romidepsin not be used in pregnancy. The sponsor has proposed Pregnancy Category D.

- Injection site reactions

The nonclinical evaluator noted dose-related local reactions in all species. Extravasation should be avoided. In the pivotal study, a central line was not required but was used at the discretion of individual investigators.

- Tert-Butyl alcohol limits

The sponsor conducted a retrospective assessment of outcomes in patients stratified by exposure to lower or higher levels of TBA. Actual differences in TBA exposure were modest (mean TBA dose in the higher exposure group, 2.5 mg/dose; mean exposure in the lower exposure group, 2.0 mg/dose), and the lower exposure group had more cumulative exposure since more cycles were given to that group. There were differences in rates of some AEs between the lower and higher exposure groups in the sponsor's retrospective analysis, but given the relatively small differences in TBA exposure, these differences in AE rates are more likely due to confounding factors. Some ECG abnormalities were more

common in the high TBA exposure group (for example, T-wave amplitude decreased, 90% versus 26%), regardless of factors such as study centre and protocol changes. While the sponsor could not rule out the influence of high TBA exposure on AEs such as decreased T-wave amplitude and QT prolongation, the differences observed in AE rates seem disproportionate given the relatively minor differences in actual TBA exposure. However, an influence of TBA has not been ruled out and TBA levels should be kept as low as possible.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of romidepsin, using the indication as proposed by the sponsor.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's OPR. The following condition of registration was advised:

- Implement EU-RMP Version 3.0 (dated 05/05/2012, DLP 31/10/2010), and Australian Specific Annex Version 1.0 (dated 08/06/2012), and any future updates.

Risk-benefit analysis

Delegate considerations

Quality of evidence: uncontrolled pivotal study

The sponsor's defence of the single arm design centres on the rarity and heterogeneity of PTCL and the absence of a standard of care for 2nd line treatment.

The clinical evaluator notes: "a Phase III trial would be more appropriate" – "but recognising the relatively uncommon nature of PTCL and ... variability in histological subtypes as well as responsiveness to therapy such a Phase III trial would have difficulties in being undertaken".

The sponsor is planning a randomised study of romidepsin in first-line treatment of PTCL in approximately 350 subjects (CHOP versus romidepsin + CHOP), despite describing this exercise as "extremely challenging". The sponsor asserts that a randomised study in relapsed or refractory PTCL would need 300-500 patients and an 8-10 year lag before final data availability; however, (a) the sponsor is already enrolling 350 patients in a first-line study and (b) interim results are often used in such a case.

The sponsor argues that there was no appropriate comparator arm available for a controlled study. Comparison with 'investigator's choice' was considered inappropriate since romidepsin activity had been observed in Study 1312, however this argument is somewhat lacking since other investigational agents also have clinical study-based evidence of activity.

Use of an IRC for review of radiographic and clinical data offsets the potential for bias arising from the open-label design.

The sponsor provided historical control comparisons, which are prone to significant bias and did not single out relevant individual regimens such as CHOP. Setting these issues aside, romidepsin appeared to produce at least equivalent complete response rates in comparison with third and fourth line therapies.

Quality of evidence: choice of primary endpoint (complete response)

The sponsor's justification of this choice is set out in the CER (see section 6.2.1 of Attachment 2 of this AusPAR).

The evaluator notes that "in Phase II trials complete response is a good indicator of likely benefit for therapy translating to improved progression free survival and overall survival". The sponsor states that use of complete response as the primary endpoint was chosen based on discussion with the FDA and lymphoma experts. A general comment is that complete response as a primary endpoint does not directly factor in the toxicity of the agent, so that complete response may be a reasonable predictor of clinical benefit only in settings where excess toxicity has been ruled out. It is accepted that complete response is a reasonable primary endpoint in this case; and in fact, those with complete response on romidepsin had substantially longer progression-free survival compared to others in the pivotal study.

Indications

The Delegate supported a modified indication as follows:

Istodax is indicated for the treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least two prior therapies.

It was acknowledged that historical comparison is a less than ideal basis on which to define risks and benefits of a medicine, but no direct comparison with relevant controls was made.

Inspection of the characteristics of complete responders in Study GPI-06-002 (PTCL) shows that 6/19 complete responders had only 1 prior therapy. Therefore, 6/38 with one prior therapy (15.8%) had a complete response, versus 13/92 (14.1%), but it is likely that current second-line treatments are more likely to be efficacious than subsequent lines, and this is borne out in the historical comparison (see Table 11 above, based on the initial cut-off).

None of the 13 patients with the rarer subtypes of PTCL achieved an objective response in Study GPI-06-0002. One patient in NCI Study 1312 with one of the rarer subtypes, enteropathy-type intestinal T-cell lymphoma (EATL), had a response to treatment. Two of the patients with relatively stable disease on romidepsin had rarer PTCL subtypes: subcutaneous panniculitis-like T-cell lymphoma and cutaneous gamma delta T-cell lymphoma; the latter patient had disease stabilisation for more than 12 months. It is reasonable not to exclude rarer subtypes from the indication.

Early stage of clinical development

The sponsor is conducting a Phase III trial in first-line treatment of PTCL (CHOP versus CHOP + romidepsin). Other post-marketing commitments [to the FDA] include a ketoconazole interaction study, a rifampin interaction study and a study in hepatic impairment, reflective of the somewhat sparse PK characterisation of the drug.

Pharmaceutical chemistry concerns

These would be resolved prior to registration. The TBA specification would ideally allow an upper limit as accepted in the USA. The sponsor notes this limit has been difficult to achieve since product approval in the USA, with levels of TBA varying in the commercial drug product. As for the risks posed by TBA, the Delegate considered them small compared to risks posed by poorly treated PTCL but it remained important to minimise them where possible.

Product Information revisions

Proposed revisions to the PI are beyond the scope of the AusPAR.

Overall benefit-risk profile

The Delegate considered there is a marginally positive benefit-risk profile in patients with PTCL who have received at least two prior therapies. The evidence base for this is not solid but the context (rare disease, etc) must be considered. Only a small proportion of subjects will attain a durable complete response with romidepsin and can be said to obtain significant clinical benefit. Relatively speaking, the toxicity of the drug is manageable, so at the population level (that is, in the group defined by the modified indication), romidepsin appears to provide a net benefit.

Proposed action

The Delegate proposed to approve the registration of romidepsin for the following (modified) indication:

Treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least two prior therapies.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request discussion of the following specific issues:

1. In what patient population, if any, does the committee see a positive benefit-risk profile for romidepsin?

A related question is whether there is any practical advantage in restricting use to PTCL patients who have received two or more prior therapies. On the one hand, weak evidence from historical comparison supports this approach. On the other hand, there is no clearly established second-line treatment for PTCL (but nor is there for first-line treatment).

2. Can the committee advise about ways to optimise the benefit-risk profile, for example, in terms of indication or provision of information in the PI?

Response from sponsor

Celgene welcomes the TGA's proposal to approve the application to register Istodax (romidepsin) in the treatment of relapsed/refractory peripheral T-cell lymphoma (PTCL), but wishes to comment on the modified indication proposed by the TGA Delegate.

Introduction

Non-Hodgkin's lymphomas are a heterogeneous group of diseases originating in various cell lines at various differentiation stages within the lymphoid system. Peripheral T-cell lymphoma is a rare form of NHL with many subtypes that share an aggressive clinical behaviour and a poor prognosis with high relapse rates following treatment. Long-term survival, especially in those who have progressed following front-line therapy, is extremely poor with 5-year overall survival rates of 32% in best cases.

In Australia, there is currently no approved treatment for patients with relapsed PTCL. Furthermore, there is no current consensus on standard therapy for PTCL in relapsed/refractory patients and there is a shortage of clinical data evaluating PTCL-specific treatment approaches. Consequently, selection of the appropriate choice of therapeutic agent remains challenging.

There is therefore an urgent unmet medical need for new therapeutic options for patients with PTCL as there is no consensus that currently available therapies improve long-term

outcomes.¹⁵ In the absence of any approved therapy for use after first relapse in the treatment of PTCL, this need becomes even greater.

Clinical evaluation – efficacy

Celgene welcomes the recommendation by the clinical evaluator to approve the use of romidepsin in the treatment of patients who have received at least one prior systemic therapy.

The proposed use of romidepsin in the treatment of relapsed PTCL patients is supported by data from a rigorously conducted (as noted by the clinical evaluator) and independently reviewed study. Results from this study demonstrate highly durable responses in relapsed patients with advanced disease, and when considered collectively in the context of historical data for other therapies, suggest a potential clinical benefit to patients with very limited options. Given the paucity of robust data for therapies after first relapse in the treatment of PTCL, the submitted data present romidepsin as a useful option in this treatment space, especially for patients unwilling or unable to receive or tolerate high dose chemotherapy or stem cell transplant. It is acknowledged that the treating physician would be ultimately best placed to determine the most appropriate treatment, based on the clinical characteristics of the individual patient. Celgene feels that these are important considerations in context of the Delegate's first question to the ACPM (*In what patient population, if any, does the Committee see a positive benefit-risk profile for romidepsin*).

The clinical trial GPI-06-0002 is considered pivotal in supporting the clinical efficacy of romidepsin in relapsed or refractory PTCL patients. The primary end-point of this study was complete response rate (including unconfirmed response rate) based on IRC assessment. Whilst acknowledging the limitations of a single-arm study, GPI-06-0002 is nonetheless the largest clinical trial conducted to date in patients with PTCL. The single-arm design is justifiable on the grounds that PTCL is a rare and heterogeneous condition and there is no established standard of care for relapsed or refractory patients, making selection of an appropriate comparator problematic. As acknowledged by the Delegate, the use of an IRC for determination of patient response offsets the potential for bias arising from the open-label study design.

As noted by the clinical evaluator, the pivotal study demonstrated impressive results in a pre-treated population (including a large proportion who had received prior autologous stem cell infusions) with a complete response rate of 14.6% and objective disease response rate of 25.4%. The response rates were consistent across patient subgroups, including across the primary histologic subtypes of PTCL. Based on the IRC assessment, the median duration of response for complete responders was estimated at 17 months suggesting a durable response. In addition, an additional IRC review conducted at a median follow-up of 22.3 months has revealed a median duration of objective response at 28 months, with the longest response ongoing at 48 months. The median duration of complete response had not been reached and achieving complete response was associated with prolonged progression-free survival and overall survival indicating further benefits in responding patients¹⁶. This long duration of response is in contrast to the duration of response of 10.1 months from the pralatrexate study. Given the aggressive nature of PTCL, the demonstrated regression of disease for a prolonged period can be considered a benefit to patients.

¹⁵ Lunning, MA, Moskowitz, AJ and Horwitz S. Strategies for Relapsed Peripheral T-Cell Lymphoma: The Tail That Wags the Curve. *J Clin Oncol* 2013;31 Published Ahead of Print as 10.1200/JCO.2012.48.3883

¹⁶ Coiffier B., Pro B., Prince M. *et al.* Romidepsin Induces Durable Responses in Patients with Peripheral TCell Lymphoma: GPI-06-0002 Study Update. Abstract of a poster presentation at the 54th American Society of Haematology Annual Medical Meeting and Exposition held December 2012.

To provide background and context in which this data has to be interpreted, Celgene also submitted a range of historical data (or External Control data) from other clinical studies and patient registries. Given the heterogeneity of patients and treatment regimens explored in those studies, this data is considered unsuitable for direct comparison or even a statistically meaningful sub-set analysis. However, the dataset nonetheless provides a useful context to evaluate the benefit of romidepsin therapy in patients with relapsed or refractory PTCL.

It is noteworthy to highlight at this point that given the inherent limitations of such a dataset, any observations derived from a comparison with historical data need to be reflective of the whole dataset rather than individual measures being considered in isolation. It would be inappropriate to base conclusions on a sub-set analysis of this comparison as the dataset is not designed for such assessment. Celgene notes the Delegate's assessment that "current second-line treatments are more likely to be efficacious than subsequent lines, and this is borne out in the historical comparison" does not appear to consider other analyses (apart from response rates) between romidepsin and other 2nd line therapies. The following observations from the historical dataset comparison should also be considered in the context of determining the efficacy of romidepsin versus other therapies in the first relapse setting.

Comparison versus other monotherapies

Monotherapy at first relapse is arguably the most appropriate treatment for the large proportion of patients who are not candidates for more aggressive or combination therapies. When compared to other monotherapies in the External Control (EC) at 2nd line, the most clinically meaningful comparison, romidepsin displayed at least similar, if not better, overall response (33% versus 27%) and complete response (18% versus 12%).

The duration of response was comparable for other EC monotherapies and romidepsin administered as 2nd line therapy with medians of 12 months noted for both sets.

Comparison versus all therapies

- Duration of response (versus all therapies)

In context of the inherent limitations in the historical dataset, the median duration of response at 2nd line was comparable between romidepsin (12 months) and all other therapies in the EC dataset (15 months).

This is a noteworthy comparison given the large imbalance in patient numbers receiving 2nd line treatment in the EC group (97 patients) versus the romidepsin group (13 patients).

The proportion of patients receiving 2nd line treatment who were event-free at 6 months was higher in the romidepsin study (83%) versus the EC dataset (71%).

- Overall survival (versus all therapies)

The median overall survival from time of first front-line therapy was better for romidepsin (34.9 months) versus all other therapies in the EC dataset (24.1 months).

For treatment at 2nd line, the median overall survival was 18.1 months for romidepsin versus 11.5 months for EC therapies.

These data suggest a benefit of romidepsin therapy in patients who have failed one prior therapy and appear to corroborate the benefit seen in the pivotal clinical trial. In addition, comparison versus the Centre for Lymphoid Cancer (CLC) database at 2nd line (literature comparison) demonstrates a comparable median progression-free survival (4 months for

romidepsin versus 3.7 months for the CLC database.¹⁷ The median PFS reported in this abstract considers selected patients with good PS of 0 or 1 only, but the pivotal romidepsin study included patients with PS > 2).

Therefore, when considering the combined 'weight-of-evidence', romidepsin appears to show useful efficacy when utilised after at least one prior therapy. A summary of the data outlined above from the historical dataset is provided in the table below:

Table 13. Summary from the historical dataset.

Key parameters for treatment at 2 nd line therapy	Romidepsin	External Control dataset
Overall Response	33%	27% (monotherapy)
Complete Response	18%	12% (monotherapy)
Median Duration of Response	12 months	15 months (monotherapy)
Event free at 6 months	83%	71%
Median Overall Survival	18.1 months	11.5 months (all therapies)

Limitations of sub-set analysis from the historical comparison

There are potential confounding factors that should be considered when interpreting sub-set results of the historical data comparison. Firstly, the patient numbers in this case are considered too low to derive meaningful comparison between romidepsin and other therapies at any line of therapy. Secondly, the responses were not assessed according to the strict International Workshop Criteria (unlike the pivotal trial) which would reduce certainty over determined response rates.

Comparison of response rates only therefore cannot be used a valid method to demonstrate inferiority (or superiority for that matter) of romidepsin versus other therapies. Whilst it is appreciated that complete response was the primary end-point in the pivotal trial, the inherent limitations of a historical comparison require that other endpoints are considered to allow a balanced interpretation.

The considerations above serve to reiterate the primary purpose of the historical comparison which is to provide a background of the current treatment landscape for PTCL. It is against this background that the results of the pivotal trial should be placed in context. The historical dataset is not designed or intended for sub-set analysis, and only a holistic interpretation of the dataset is likely to provide meaningful assessment of the value of using romidepsin at first relapse.

Limitations of current treatment options after first relapse

It is noted that when comparing the complete response between romidepsin and other EC therapies at 2nd line in the historical dataset, the results appear to favour other therapies. However, the inherent limitations of the historical dataset notwithstanding, it is also worth considering that in the current treatment paradigms for PTCL, high response rates are not necessarily reflective of better long-term patient outcomes. As reported by Lunning *et al.*¹⁵, combination chemotherapies may result in higher response rates but such therapies are usually tolerated only for a low number of cycles due to toxicity. Notable examples provided by the authors include treatment with ICE (ifosphamide, carboplatin, and etoposide) which yielded response rates of 70% but the median progression-free survival was less than 6 months (in 40 patients), or use of Gem-P (gemcitabine, cisplatin, and methylprednisolone) which yielded an overall response rate of 69%, but time to progression was only 4 months (in 16 patients). Despite the low patient numbers, this

¹⁷ Mak, V., Hamm, J., Chhanabhai M. et al. Survival of Patients With Peripheral T-Cell Lymphoma After First Relapse or Progression: Spectrum of Disease and Rare Long-Term Survivors. *J Clin Oncol.* 2013;31. Published on-line ahead of print on April 22, 2013 as 10.1200/JCO.2012.44.7524.

trend appears to be prevalent across multiple combination therapy options. Therefore, such therapies are useful as induction or bridging strategies to more definitive treatments such as allogeneic stem cell transplant but in isolation, they do not seem to offer long term benefit in terms of durable response and progression-free survival. This is also highlighted by the negligible difference in progression-free survival between all patients and those who received 2nd line therapy in the CLC dataset, and is in contrast to romidepsin which can be delivered in a more continuous fashion thus allowing long term disease control.¹⁵

Considering therefore that around 82% of patients in the EC dataset received combination therapy or underwent high dose therapy with SCT at 2nd line, it is not unexpected that the response rates in these patients were better compared to patients who received romidepsin at 2nd line. However, romidepsin has been demonstrated to provide durable responses with a median duration of 28 months and responses of up to 48 months (compared to 10.1 months for pralatrexate) and together with its manageable safety profile, may serve as a more viable continuous treatment option for patients which may lead to better long-term outcomes. This is consistent with the assessment by Lunning et al.¹⁵ who state that “outside of a curative approach (allogeneic transplantation), the best chance at achieving a durable response is through a continuous treatment approach”.

Whilst it is agreed that high dose therapy with SCT would be a preferred option at first relapse for curative intent, the efficacy is offset by a high treatment-related mortality rate, primarily related to infections and, for allogeneic transplant, graft versus host disease.¹⁸ Secondly, based on expert opinion, only 25% of first relapse patients are eligible for SCT. This means that a majority of first relapse patients are in need of well-tolerated and effective continuous therapy which can provide durable response and better long-term outcomes compared to existing therapies.

Risk-benefit profile

Celgene strongly believes that a positive benefit to risk ratio for romidepsin is demonstrated for use after at least one prior therapy:

- Romidepsin has demonstrated efficacy in relapsed or refractory PTCL, a highly-aggressive and difficult to treat malignancy.

Specifically, in the assessment-blinded clinical study, romidepsin shows high rates of durable complete responses in a group of patients that require second-line and later therapy and have no satisfactory treatment options available to them. Furthermore, patients who achieve clinical response derive benefit from the response in the form of prolonged progression-free survival and overall survival compared with patients who do not achieve this level of response.

In addition to the pivotal clinical study results, holistic comparison with a historical dataset provides a useful gauge versus other therapies and romidepsin is shown to have comparable benefits against medically relevant therapies at 2nd line.

- Romidepsin has a well-defined and manageable safety profile in relapsed or refractory PTCL.

The safety profile is supported by the largest existing safety database in relapsed or refractory PTCL consisting of 178 patients, with additional supportive safety data in more than 800 patients. The safety profile of romidepsin is generally predictable and manageable. The main risks consist of haematological toxicity and secondary infections or haemorrhagic complications, which are consistent with other chemotherapeutic agents. The risk of Grade 3-4 haematological adverse reactions was lower compared to other treatment agents, and similar for other Grade 3-4 toxicities.

¹⁸ Ramsdale E, Van Besien K. Allogeneic transplant for peripheral T-cell lymphoma: a sparkle of hope and many questions. *Leuk Lymphoma* 2011;52(6):938-940.

Romidepsin also exhibited a better safety profile compared to pralatrexate with a lower incidence of Grade 3-4 adverse events, and with pralatrexate treatment resulting in the occurrence of mucositis, higher incidences of Grade 3 and 4 haematologic AEs, greater frequency of liver function test elevations, and the occurrence of fatal dermatologic reactions in comparison to romidepsin treatment. This better safety profile may facilitate longer continuous treatment with romidepsin than with pralatrexate, allowing for potential better long-term outcomes.

In addition to the USA FDA approval of romidepsin for treatment of PTCL patients who have received at least one prior therapy, romidepsin has also been recently listed as a recommended first relapse treatment option in the National Comprehensive Cancer Network (NCCN) 2013 guidelines¹⁹. This is significant international recognition by specialist guidelines (as determined by expert centres) that romidepsin should be considered as an appropriate and effective treatment after at least one prior therapy. Celgene would like to therefore highlight that the modified indication proposed by the TGA Delegate for use after two prior therapies would be inconsistent with current internationally adopted recommendations for PTCL treatment, and may deny a treatment option to appropriate patients as determined by the treating physician on a case-by-case basis.

Proposed indication

The modified indication proposed by the TGA Delegate is as follows: *Istodax is indicated for the treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least two prior therapies.*

Celgene believes that sufficient evidence has been presented to support the original indication outlined in the application and as shown below:

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

The data provided demonstrate durable responses in patients who have received prior therapy and, when the entire 'body-of-evidence' is considered, provide an indicator of clinically meaningful benefit of romidepsin use after at least one prior systemic therapy. Importantly, the proposed indication will provide physicians with an additional option in their therapeutic armamentarium to use earlier in the treatment of appropriate patients in a condition where relapse is virtually certain and where current therapeutic options do not appear to significantly improve long-term patient outcomes.

Pharmaceutical chemistry evaluation

The TGA Delegate also raises the issues of impurity limits for the drug substance and limits of residual *tert*-butyl alcohol.

Celgene agrees to tighten the drug substance limit for an unknown impurity. Celgene also agrees to tighten the finished product limit for residual *tert*-butyl alcohol.

Amendment of the product information

A number of changes to the PI were requested during the evaluation of this application, including some suggested by the TGA Delegate. Celgene has updated the PI to reflect most of these requested changes. Some changes have been deferred for further discussion at the PI negotiation stage.

¹⁹ National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology (NCCN Guidelines) Non-Hodgkin's Lymphomas. Version 1.20 13. 18 December 2012.

Conclusion

To summarise, romidepsin has displayed clinically meaningful efficacy and predictable and manageable safety profile in relapsed PTCL patients, in a rigorously conducted study setting. Evidence of comparable efficacy versus medically-relevant therapies has also been indicated from a historical control comparison. Assessment of this 'weight-of-evidence' suggests a valuable role for the use of romidepsin after at least one prior therapy. Considering recent literature highlighting the need for therapies with durable, rather than strong but short-lived, responses, and given the difficulties associated with conducting a controlled Phase III study for conditions as rare and heterogeneous as PTCL, these data provide considerable support for use of romidepsin after at least one prior systemic therapy.

The main risks associated with romidepsin therapy consist of cytopenias and secondary infections or haemorrhagic complications, risks common to other therapies used to treat this condition. The risk from toxicity is therefore not greater than with any other chemotherapy treatment and has shown to be lower than some other therapies including pralatrexate, potentially allowing longer continuous treatment for better outcomes.

Furthermore, in addition to FDA-approved use after at least one prior therapy, romidepsin has also been recognised as a valid option for treatment after first relapse in the NCCN guidelines. This is a significant indicator that romidepsin is now internationally recognised by specialist guidelines as an appropriate treatment option for relapsed PTCL.

In conclusion, given the noteworthy efficacy and established safety results, which allow for a positive benefit to risk ratio to be determined in a well defined PTCL patient population, and the fact that there are currently no approved therapies or therapies supported by robust clinical studies available for patients with treatment-refractory PTCL in Australia, Celgene considers that romidepsin offers a valuable treatment option for a group of PTCL patients with a clear unmet medical need.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Istodax (containing romidepsin) to have an overall positive benefit-risk profile for the delegate's amended indication;

Treatment of patients with peripheral T-cell lymphoma (PTCL) who have received at least one prior therapy

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A clear statement in the relevant section of the PI and the CMI that the optimal treatment of patients obtaining complete response is to proceed to haemopoietic stem cell transplant.

- A statement in the Precautions section of the PI and relevant sections of the CMI to reflect the poorer outcome in patients with lower performance scores, based on the report in Mak, V. *et al.*, JCO.²⁰

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Istodax (romidepsin) 10 mg powder for injection vial, and solvent for reconstitution vial, indicated for:

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

Specific conditions applying to the therapeutic good

- The Istodax EU-Risk Management Plan (RMP), version 3.0, dated 5/5/2012, and Australian-specific Annex Version 1.0, dated 8/6/2012, included with submission PM-2012-01446-3-4, and any subsequent revisions as agreed with the TGA's Office of Product Review, will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

²⁰ This refers to the publication provided in the sponsor's pre-ACPM response: Mak, V., Hamm, J., Chhanabhai M. *et al.* Survival of Patients With Peripheral T-Cell Lymphoma After First Relapse or Progression: Spectrum of Disease and Rare Long-Term Survivors. *J Clin Oncol.* 2013;31. Published on-line ahead of print on April 22, 2013 as 10.1200/JCO.2012.44.7524.

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