

**5.13 ROMIDEPSIN,
Powder for I.V. infusion 10 mg,
Istodax[®],
Celgene Pty Ltd.**

Application submitted by Rare Cancers Australia

Rare Cancers Australia lodged a submission to the November 2016 PBAC meeting for histone deacetylase (HDAC) inhibitor therapies for the treatment of relapsed/refractory T-cell lymphoma. This submission requested PBS listing of two drugs: romidepsin and vorinostat (item 7.11 refers). During the evaluation process, two commentaries were prepared to enable thorough consideration of the effectiveness, safety and cost-effectiveness of each drug. The current document provides the PBAC consideration of the evidence submitted for romidepsin.

1 Purpose of Application

1.1 Section 100, Authority Required listing for romidepsin for treatment of relapsed or chemotherapy refractory peripheral T-cell lymphoma (PTCL).

2 Requested listing

2.1 The submission requested an Authority Required listing (via Section 100, Highly Specialised Drugs Program) for romidepsin for the treatment of relapsed or chemotherapy refractory PTCL in patients who: have received and failed prior systemic therapy; are not candidates for a stem cell transplant; and will not receive concomitant treatment with other systemic therapies.

2.2 An abridged version of the proposed listing is presented below, which omits the Administrative Advice, including the notes that no increase to the maximum quantity or repeats will be authorised. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out in strikethrough.

<i>Name, Restriction, Manner of administration and form</i>	<i>Max. Amount</i>	<i>No. of Rpts</i>	<i>Ex-manufacturer price per vial</i>	<i>Dispensed Price for Maximum Amount (DPMA)^a</i>	<i>Proprietary Name and Manufacturer</i>
ROMIDEPSIN romidepsin 10 mg injection [1 vial] (& inert substance diluent [2 mL vial], 1 pack	31 mg	17	Listed: \$ [REDACTED] Pricing arrangement: \$ [REDACTED]	\$ [REDACTED] (Private) \$ [REDACTED] (Public)	Istodax® Celgene Pty Ltd

^a These DPMA's assume a distribution fee of \$25.92, a diluent fee of \$5.14 and a preparation fee of \$103.22 (see <https://www.pbs.gov.au/info/browse/section-100/chemotherapy>). These numbers have been updated as of 11th August

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2016.

Category / Program	Section 100 – Highly Specialised Drugs Program Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or refractory
Condition:	Peripheral T-cell lymphoma
PBS Indication:	Relapsed or chemotherapy refractory peripheral T-cell lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be for curative intent, AND Patient must have undergone appropriate prior front-line curative intent chemotherapy, AND Patient must demonstrate relapsed or chemotherapy-refractory disease, Patient must have received and failed prior systemic therapy, AND Patient must not be a candidate for a stem cell transplant, Patient must be ineligible for a primary stem cell transplantation, AND The treatment must not be used in combination with other systemic therapies The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed PTCL romidepsin PBS Authority Application - Supporting Information Form [to be determined] which includes the following: (i) The date of initial diagnosis of PTCL a histological diagnosis of relapsed or chemotherapy-refractory peripheral T-cell lymphoma; (ii) Dates of commencement and completion of prior systemic therapy or therapies; (iii) details of prior treatment including name(s) of drug(s) and date of most recent treatment cycle; and (iv) a declaration of the patients ineligibility for primary stem cell transplant. (iii) a declaration of whether the patient's disease is relapsed or refractory,

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	and the date and means by which the patient's disease was assessed as being relapsed or refractory.
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic
Clinical criteria:	Patient must have previously qualified for PBS subsidised romidepsin, and remains free from progressive disease And The treatment must not be used in combination with other systemic therapies <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition,</i> <i>AND</i> <i>Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition,</i> <i>AND</i> <i>The treatment must be a sole PBS-subsidised treatment with this drug for this condition.</i>

- 2.2 The “DPMQ” proposed in the submission was a fixed ex-manufacturer price per vial, excluding fees. During the evaluation, the DPMA was calculated on a dispensed price basis. In calculating the DPMA, the evaluator assumed an ex-manufacturer price per vial of \$██████, consistent with ███% of the ex-manufacturer price as reported in the PB11b form provided by the applicant. In a letter accompanying the submission, Celgene confirmed it was seeking a special pricing arrangement with a published list price of \$██████ per 10 mg vial, with an effective price of \$██████ per 10 mg vial, representing a ███% discount.
- 2.3 The submission did not include a maximum amount or maximum number of repeats in the proposed PBS listing. The Secretariat proposed that the maximum amount for one dose should be 31 mg, as this would provide sufficient amount for a patient with a BSA of up to 2.2 m². The Secretariat proposed that there should be 17 repeats, as this would allow sufficient drug for treatment duration of 6 months under either Initial or Continuing criteria.
- 2.4 The submission requested grandfathering of patients currently receiving romidepsin via an Expanded Access Program. Currently, 20 PTCL patients receive romidepsin through expanded access.
- 2.5 Based on the evidence presented in Section B of the resubmission, the requested basis for listing is cost-effectiveness compared with “no active treatment”.
- 2.6 The PBAC noted the proposed restriction and:

- considered that the aim of romidepsin treatment in the proposed PBS population was not curative, but to safely induce prolonged remission without adversely affecting a patient's quality of life. As such, the PBAC advised that the criterion "The treatment must be for curative intent" should be removed from the initial treatment criteria;
- considered that continuing treatment should be restricted to patients who demonstrate an objective response to initial treatment with romidepsin, given that the data presented in the resubmission indicated that benefit from romidepsin treatment was confined to responders.
- considered that therapies other than chemotherapy may be used as first-line treatment, and recommended that the Secretariat proposed criterion should be changed to "Patient must have undergone appropriate prior front-line ~~curative intent chemotherapy~~ systemic therapy".
- considered that romidepsin may be used as a bridging therapy to transplantation (see "Clinical place of the proposed therapy"), and that the criterion "Patient must be ineligible for a stem cell transplantation" might not be appropriate.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 **TGA status at the time of PBAC consideration:** romidepsin was TGA registered on 07 August 2013 for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy
- 3.2 Romidepsin has not been considered by the PBAC previously.
- 3.3 Romidepsin is an inhibitor of class I and II histone deacetylase enzymes (HDACs). HDACs regulate a variety of cell functions involved in cell survival, cell cycle progression, angiogenesis, and immunity.

4 Clinical place for the proposed therapy

- 4.1 PTCL comprises a group of heterogeneous non-Hodgkin lymphomas that develop from T-cells in different stages of maturity.
- 4.2 The submission proposed PBS listing for romidepsin for PTCL patients who have previously received and failed prior systemic therapy and are not a candidate for a stem cell transplant.
- 4.3 The ESC considered that some uncertainty remained around the clinical place of romidepsin in treating PTCL. The ESC noted that romidepsin may be used as a 'bridging therapy' to stem cell transplant if it can provide a patient who is ineligible for transplant at the time of treatment with sufficient disease control to proceed to transplantation while remaining in complete remission. The ESC also noted that the TGA registration for romidepsin did not restrict use to relapsed or refractory disease. The PBAC agreed with ESC that romidepsin could be used as bridging therapy to transplantation, and that this may be an important use of this drug in Australian

practice.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated "no active therapy" as the main comparator. The ESC agreed with the commentary that "standard of care" would be a more appropriate comparator. The ESC noted that there are other treatments for relapsed or chemotherapy refractory PTCL that have efficacy rates in the same range as those cited for romidepsin in a similar patient population (in a naïve indirect comparison) (*Blood* 2014, 123(17), 2636-2644, see Table 4). These treatments could be replaced or delayed for some patients if romidepsin was PBS subsidised. The ESC considered that other active therapies would be either replaced or displaced by romidepsin should it be listed. If a patient was not fit for further active therapy, they would likely not be fit for romidepsin. The PBAC agreed with the ESC and noted that romidepsin may be used earlier in the treatment algorithm for some patients on the basis of its toxicity profile or as a bridging therapy to transplantation.
- 5.2 The ESC noted the comments in the Pre-Sub-Committee Response about alternative treatments and clinical need, and considered that the availability of active treatments does not mean that there cannot also be high clinical need in a disease area. In the case of relapsed or refractory T-cell lymphoma, the ESC considered there was a clinical need for new treatments as although currently available active treatments are likely to have some benefits they do not result in cure or long term remission.
- 5.3 While the resubmission argued for "no active therapy" as the comparator, survival in the comparator arm of the economic evaluation was based on Australian registry data from patients who did not respond to HDAC inhibitors. These patients had received a variety of other systemic treatments before and after the HDAC inhibitor. Therefore, the economic evaluation essentially compared patients who received an HDAC inhibitor following other active treatments with patients who received (but did not respond to) an HDAC inhibitor and other active treatments.
- 5.4 The Pre-PBAC response (p1) claimed that given the limitations of the available clinical evidence, an inactive comparator was the best way forward to provide PBAC with a rationale for considering a new treatment for this disease. The PBAC noted ESC's concerns regarding "no active therapy" being the nominated comparator but considered that if recommended for PBS listing, romidepsin would be used to displace, rather than replace currently available treatments, which vary widely in nature and applicability to individual cases. As such, the PBAC viewed that "no active therapy" could reasonably be considered a comparator. Regardless, the PBAC noted that no comparative analysis against either comparator was presented.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 The applicant, Rare Cancers Australia, requested a hearing for this item. At the hearing, representatives from the organisation acknowledged the limitations of the available data and urged the PBAC to consider the submission in the light of PTCL being an uncommon form of cancer and the unmet need for a PBS-subsidised HDAC inhibitor to treat this malignancy. The PBAC noted Rare Cancer Australia's advice on its interactions with the sponsors of the two drugs presented in this submission [item 7.11 vorinostat refers], and considered that the hearing was informative as it provided further background on an unconventional submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments noted support for availability of this drug and a hope for improved quality of life under treatment. The PBAC noted the advice from Rare Cancers Australia, which included feedback from patients about how romidepsin treatment provided additional time with loved ones, a new line of therapy after chemotherapy and stem cell transplant, fewer side effects than chemotherapy, and an improved quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 Representatives of the PBAC also met with Rare Cancers Australia prior to the PBAC meeting. The meeting covered the PBAC consideration of romidepsin for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) and vorinostat for the treatment of patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL) (item 7.11 vorinostat refers). The November 2016 meeting was the PBAC's first consideration of romidepsin and second consideration of vorinostat for these conditions. The following points provide a summary of the perspectives presented by Rare Cancers Australia to PBAC representatives:
- There are currently limited treatment options for patients with relapsed or refractory PTCL and CTCL, and available treatment options have high toxicity.
 - The physical manifestations of the condition have a profound effect on patients' quality of life. In particular the impact of ulcerated lesions associated with CTCL on patients, including lesion pain, frequent need for painful local treatment, and the cost of associated consumables (for instance bandages and dressings) were described.
 - Romidepsin and vorinostat are offered to some patients currently, but (unless the patient is able to access treatment through a clinical trial) this is at a very high cost to the patient. Patients consider that this is inequitable.
 - Patients consider romidepsin to be mostly well tolerated, noting that side effects had been transient, manageable, or able to be resolved with reduction of dose.

Clinical trials

- 6.4 The submission is based on two key, single-arm Phase II studies (Study 0002, n=130 and Piekarz 2011, n=47) of romidepsin in PTCL.
- 6.5 A number of supplementary, single-arm studies (two of romidepsin in cutaneous T-Cell Lymphoma (CTCL) and two of vorinostat in CTCL) are also presented but are not used as the basis of the clinical claims in the submission or the subsequent economic evaluation.

- 6.6 The efficacy and safety data were difficult to assess in the absence of a comparative analysis. The ESC noted that in the absence of comparative data, the effectiveness and safety of the comparator arm would usually be informed by other types of data, for instance: historical controls, registry data, or other single arm studies. The ESC further noted that application to the TGA for registration of romidepsin included a comparison of with historical controls. This analysis was not provided in the PBAC submission. The PBAC would have welcomed assessment of this analysis, particularly as a means of establishing if currently available treatments offer meaningful benefits to patients, and placing the durable responses in some patients with PTCL in context.
- 6.7 Details of the key romidepsin trials presented in the submission are provided below.

Table 1: Trials and associated reports presented in the submission

Study	Description	Reports
Romidepsin in PTCL		
<i>Nonrandomised studies (key)</i>		
Study 0002	Prospective, multinational, single arm, phase II study	<p>A Phase II, multicenter, open-label study evaluating the activity and tolerability of romidepsin (Depsipeptide FK228) in progressive or relapsed peripheral T-cell lymphoma following prior systemic therapy. 11 November 2010.</p> <p>Coiffier B, Pro B, Prince HM, Foss F, 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. <i>J Clin Oncol</i> 2012; 30(6):631-636.</p> <p>Coiffier B, Pro B, Prince M, Foss FM, et al. Romidepsin induces durable responses in patients with peripheral t-cell lymphoma: GPI-06-0002 study update. <i>Blood</i>, 2012; 120(21): 3641.</p> <p>Coiffier B, Pro B, Prince HM, Foss F, et al. Analysis of patients with common peripheral T-cell lymphoma subtypes from a Phase 2 study of romidepsin in relapsed or refractory peripheral T-cell lymphoma. <i>Blood</i> 2011; 118(21):591.</p> <p>Coiffier B, Pro B, Prince HM, Foss FM, et al. Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy. <i>Blood</i> 2010; 116(21):114.</p> <p>Coiffier B, Pro B, Prince HM, Foss F, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. <i>Journal of Hematology & Oncology</i> 2014; 7(1):1.</p> <p>Foss F, Horwitz S, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/ refractory peripheral T-cell lymphoma: prolonged stable disease provides clinical benefits for patients in the pivotal study. <i>Journal of Hematology & Oncology</i> 2016; 9(1):1.</p>

Study	Description	Reports
Piekarz 2011	Prospective, multi-institutional, single arm, phase II study	<p>Piekarz RL, Frye R, Prince HM, Kirschbaum MH, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. <i>Blood</i> 2011; 117(22):5827-5834.</p> <p>Piekarz R, Wright J, Frye R, Allen SL, et al. Final results of a Phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphoma (PTCL). <i>Blood</i> 2009; 114(22):1657.</p> <p>Piekarz RL, Frye R, Turner M, Turner J, et al. Phase II trial of romidepsin (FK228 or depsipeptide) in peripheral T-cell lymphoma: clinical activity and molecular markers. <i>Haematol Rep</i> 2006; 2(13):29-31.</p>

Source: Table 16, pp 66-68 of the submission.

6.4 The key features of the key clinical studies are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Romidepsin in PTCL						
Study 0002	130	N-R, MC, OL 48 mths	High	Relapsed/refractory	Response rate, DOR, PFS, OS, toxicity	Yes (response rate)
Piekarz 2011	47	N-R, MC, OL 74 mths	High	Relapsed/refractory	Response rate, DOR, pharmacokinetics, toxicity	No

Source: compiled during the evaluation

Abbreviations: DOR, duration of response; MC, multi-centre; N-R, non-randomised; OL, open label; OS, overall survival; PFS, progression-free survival.

6.5 The ESC considered it important to note that performance status in both key clinical trials was ≤ 2 , the minimum life expectancy in Piekarz 2011 was 12 weeks, and patients in both studies had adequate bone marrow and organ function. The proposed PBS population could include patients with a worse performance status and/or life expectancy and/or bone marrow/organ function as these criteria are not specified in the PBS listing. The performance status and baseline characteristics of Australian PTCL patients are unknown. Whether baseline clinical characteristics affect the efficacy and/or safety of romidepsin is also unknown.

Comparative effectiveness

6.6 No comparative effectiveness data were presented. Effectiveness measures for romidepsin, obtained from the key clinical studies, are provided in Table 3 below.

Table 3: Effectiveness of romidepsin in the key clinical studies

Trial ID	Objective response rate n with event/N (%)	Time to response Median (range) in months	Duration of response Median (range) in months	Time to progression (TTP) / progression free survival (PFS) Median in months	Overall median survival in months
Study 0002	33/130 (25)	1.8 (1.4-5.3)	6.6 (<0.1-34)	PFS, all: 4 CR/CRu: 18 PR: 7 SD: 6 PD: <2	Update (Coiffier et al. 2014), CR/CRu+PR: 30 (2.0-49.5)
Piekarz 2011	17/45 (38)	1.8 (<2-11)	8.9 (2-74)	TTP, CR+PR: 13.0 SD: 4.6 PD: 1.4	NR

Source: Table 27, pp 104-105 of the submission.

Abbreviations: CR, complete response; CRu, complete response unconfirmed; NR, not reported; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; TTP, time to progression.

- 6.7 Given that the studies had only one treatment arm, information about the comparator and absolute or relative differences was not available.
- 6.8 Both studies had response rate as the primary outcome. Survival was reported in an updated analysis of Study 0002, but was not used in the base case of the economic evaluation. For the economic evaluation, survival outcomes for responders/non-responders were applied to the proportion of responders observed in Study 0002 using a surrogate relationship inferred from Australian registry data.

Comparative harms

- 6.9 No comparative safety data were presented. All safety data originated from non-randomised, single arm, open-label studies. In Study 0002, the most frequent grade ≥ 3 adverse events were thrombocytopenia (23%), neutropenia (18%), leukopenia (6%), asthenia/fatigue (6%) and infections (6%). Other frequent adverse events (which were seldom grade 3 or 4) included nausea, vomiting and diarrhoea.
- 6.10 The ESC noted that harms were measured in the context of clinical trials which required patients to have a performance status of ECOG ≤ 2 at baseline. This was inconsistent with the proposed PBS patient population, which could include patients with a worse performance status, and therefore at greater risk of severe toxicity.

Benefits/harms

- 6.11 A summary of the benefits and harms for romidepsin is presented below. Comparative information on benefits or harms was not available given the lack of comparative studies.

Table 4: Summary of benefits and harms for romidepsin

Trial	Romidepsin	No active treatment	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Romidepsin	No active treatment	
Benefits (objective response)						
Dichotomous Outcome I						
Study 0002	33/130	NE	NE	25	NE	NE
Piekarz 2011	17/45	NE	NE	38	NE	NE
Harms						
	Romidepsin	No active treatment	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Romidepsin	No active treatment	
Grade ≥ 3 thrombocytopenia						
Study 0002	30/130	NE	NE	23	NE	NE
Piekarz 2011	7/45	NE	NE	15	NE	NE
Grade ≥ 3 leukopenia						
Study 0002	8/130	NE	NE	6	NE	NE
Piekarz 2011	14/45	NE	NE	30	NE	NE
Grade ≥ 3 granulocytopenia						
Study 0002	NR	NE	NE	NR	NE	NE
Piekarz 2011	12/45	NE	NE	26	NE	NE
Grade ≥ 3 neutropenia						
Study 0002	24/130	NE	NE	18	NE	NE
Piekarz 2011	8/45	NE	NE	17	NE	NE

Source: Compiled during the evaluation

Abbreviations: CI, confidence interval; NE, not evaluable; NR, not reported; RD, risk difference; RR, risk ratio

^a Maximum duration of follow-up: Study0002 = 34 months (at cut-off Oct 2010); Piekarz 2011 = 74 months.

Clinical claim

- 6.12 The submission described romidepsin as superior in terms of comparative effectiveness and marginally inferior in terms of comparative safety over no active therapy. This claim was not well supported by the data presented. The key studies presented in the submission were non-randomised, single arm, open-label studies. As such, the studies were subject to considerable bias, the effectiveness estimates refer only to romidepsin and not its comparative treatment effect or safety, and were subject to considerable uncertainty. The ESC considered that the clinical claim could not be reliably assessed in the absence of data for the comparator arm.

- 6.13 The TGA Delegate concluded that “there is a marginally positive benefit-risk profile in patients with peripheral T-cell lymphoma (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”.
- 6.14 The PBAC noted the updated information provided in Coiffier *et al.*, 2014¹ on the durability of benefit in responders, and considered that for a sizeable minority of patients, a durable response could be achieved with romidepsin. The PBAC considered it likely that romidepsin had superior comparative effectiveness over “no active therapy”; however the magnitude of any benefit was uninterpretable due to the limited and biased nature of the data.
- 6.15 At the same time, the PBAC remained concerned about the heterogeneity of the PTCL patient population and the lack of evidence of underlying biological characteristics to explain the observed responses. The PBAC was consequently uncertain as to the applicability of the trial results to the various PTCL subtypes.
- 6.16 The PBAC considered that romidepsin was likely to be effective in the treatment of CTCL, and would welcome comparative clinical evidence to support assessment of this claim.
- 6.17 The PBAC noted that the adverse events reported were from patients with ECOG performance status ≤ 2 . Patients in the proposed PBS population could have a worse performance status, and therefore be at greater risk of harm. The PBAC considered that the claim of inferior safety compared with no active therapy was reasonable.

Economic analysis

- 6.18 The use of a cost-effectiveness model in the submission presupposes that the claim of clinical superiority is acceptable. As noted above, the comparative effectiveness of romidepsin could not be reliably assessed in the absence of data for the comparator arm. The PBAC considered that a comparative analysis was necessary to enable an assessment of the cost-effectiveness of a romidepsin listing for PTCL.
- 6.19 The submission provided a modelled cost-utility analysis, see Table 5.

Table 5: Summary of model structure and rationale

Component	Summary
Time horizon	The maximum time horizon was based on the observed median survival of 46.4 months in responders in the Australian registry data. In that registry, survival was assessed using Kaplan-Meier analyses with a maximum of 7.7 years follow-up.
Outcomes	QALYs, costs

¹ Coiffier *et al.*, 2014, “Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses”, *Journal of Hematology & Oncology* 7:11, DOI: 10.1186/1756-8722-7-11.

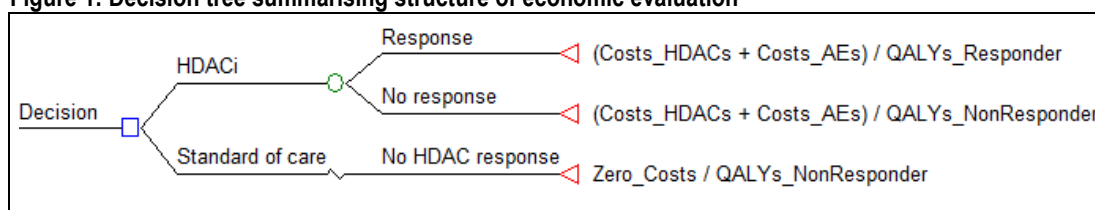
Component	Summary
Methods used to generate results	Translation from response to survival, with the application of utility values from HL and sALCL on the basis of patients' responder status. A decision tree analysis was performed.
Clinical inputs	Probability of response was assumed to be 0 for the comparator, and 0.25 for romidepsin (as obtained from Study 0002). Discounted PFS was 0.24 years for the comparator and 0.81 years for romidepsin, based on Australian registry data. Discounted OS was 0.30 years for the comparator and 1.10 years for romidepsin, based on Australian registry data.
Discount rate	5% for outcomes, costs were not discounted.
Software package	Microsoft Excel (version not reported)

Source: compiled during the evaluation

Abbreviations: HL, Hodgkin's lymphoma; OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life years; sALCL, systemic anaplastic large-cell lymphoma.

- 6.16 The use of the Australian registry data, and particularly the use of data from patients who did not respond to HDAC therapies (and who had received a variety of other therapies before and after the HDAC therapy), essentially compares patients who received an HDAC inhibitor following other active treatments with patients who received but did not respond to an HDAC therapy (and other active treatments). The ESC considered that this was a fundamental problem with the structure of the model.

Figure 1: Decision tree summarising structure of economic evaluation



Source: Figure 28, p 150 of the submission.

Abbreviations: AEs, adverse events; HDACi, histone deacetylase inhibitor; HDACs, histone deacetylase inhibitors; QALYs, quality-adjusted life years.

- 6.17 The ESC noted that the approach to modelling survival effectively biases the estimated survival of the 'no active treatment' arm, by selecting patients who progressed or died within 6 months of receiving a HDAC inhibitor (thereby ensuring progression free survival in this arm of less than 6 months). By contrast, responders are selected on the basis of a time to next treatment of greater than 6 months. This meant that the model assumed:

- all responders have a minimum survival of 6 months.
- there were no responders in the 'no active treatment' arm.

Both of these assumptions bias the survival rates in favour of romidepsin, and were not well justified in the submission and PSCR. The PBAC recognised the intent of the approach as explained in the submission, PSCR and pre-PBAC response to model outcomes in the absence of romidepsin, but like ESC, considered that the model was flawed and was not informative to the assessment of cost effectiveness.

- 6.18 Response rates for romidepsin treated patients were obtained from Study 0002. The submission did not compare baseline characteristics of the study population to the

expected PBS population. Patients in the romidepsin studies were likely to have a better prognosis than the expected PBS population, given that study entry criteria were based on adequate performance status, life expectancy and organ function, while the proposed PBS eligibility criteria are not.

- 6.19 Australian registry data were used to determine survival outcomes on the basis of response. These analyses did not differentiate between the different types of HDAC inhibitors used by patients in that registry. The results are therefore not specific to romidepsin in PTCL (n=18), but also include patients treated with vorinostat (n=4) and panobinostat (n=8) in PTCL. No information is provided to assess whether survival observed following other HDAC inhibitors can be used as a proxy for romidepsin. The PBAC noted that the PTCL database results included 30 patients whilst the CTCL database results included 67 patients. Given that PTCL represents a broader population than CTCL (a T cell lymphoma subtype), but the registry provided a smaller sample size, the PBAC questioned the overall relevance of the registry data for modelling the cost-effectiveness of treatment for PTCL. Rather, the PBAC considered that the registry data might be of greater relevance for assessing treatment in the context of CTCL.
- 6.20 For the economic evaluation, a surrogate relationship was assumed to apply between response in PTCL and the median durations of PFS and OS from the registry. This translation from a surrogate outcome (response) to a final outcome (survival) was not sufficiently substantiated in the submission. The submission only provided data from Study 0002 and the registry to support the application of the relationship between response and survival. The ESC noted from the PSCR (p3) that “Coiffier et al (2014) established a link between response to romidepsin and overall survival in patients with PTCL. The Australian registry data were then used to investigate whether this relationship between response to HDAC inhibitor and overall survival would hold in Australian patients with either CTCL or PTCL.”
- 6.21 Patients with a time to next treatment (TTNT) \geq 6 months were considered to have received a meaningful treatment benefit and were classified as “responders”. The ESC noted that clinically, this would be considered a response in this disease. However, this definition of response ensures that all responders in the model have a minimum survival of six months, while non-responders could die within six months. This, along with the assumption of a 0% response rate in the comparator arm, biases survival in favour of the romidepsin arm. The ESC considered that neither of these assumptions were well justified in the submission and PSCR. Furthermore, using TTNT as a proxy for PFS is problematic because it does not account for switching for other reasons (besides non-response), or patients who progress but do not switch treatments.
- 6.22 The Australian registry data showed that the median Overall Survival (OS) for non-responders was 3.7 months while the median OS for responders was 46.4 months (p=0.0122). Median TTNT (as a proxy for PFS) was 3.0 months for non-responders versus 32.8 months for responders (p=0.0001). An OS of 46.4 months in patients responding to treatment is extremely high given the natural history of PTCL. Data from the Surveillance, Epidemiology, and End Results (**SEER**) Program of the National Cancer Institute database indicate a median OS of 26 months (not-stratified for response) for PTCL patients. The PSCR (p4) noted that the median survival in the registry was 33.9 months when the data are not stratified by response.

- 6.23 The economic evaluation applied the survival of non-responders to all patients in the comparator arm. This is not appropriate since not all patients receiving “no active treatment” would be expected to progress within six months. The PSCR (p4) argued that “advanced PTCL is generally considered a very aggressive disease. While not unheard of in a subgroup of PTCL (AITL) spontaneous remission is rare (Humenuik et al, 2014: 27(3):242-245).”
- 6.24 The types and order of treatments may have influenced the benefit accruing to patients in the registry. There are insufficient data to evaluate the effect on response and survival of differences in the timing of HDAC inhibitors, the number of prior therapies, or indeed the HDAC inhibitors with which patients were treated.
- 6.25 The Pre-PBAC response (p2-3) acknowledged the confounding and bias involved in using the registry data in the economic model, but argued that this was a reasonable approach for assessing the potential value of response, as responders and non-responders were well-matched at baseline in terms of key clinical and demographic characteristics.
- 6.26 Utility values in the economic evaluation were obtained from Swinburn et al. 2015, a study in relapsed/refractory Hodgkin’s lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL), which is a subtype of PTCL. The selected utility values may not represent the patient experience for all PTCL histologies. However, given the lack of published utility values the selection of utility values is reasonable.
- 6.27 The economic evaluation included the costs of romidepsin, drug administration costs and treating adverse events. Disease management costs were not considered. The submission excluded these costs for simplicity and because they were assumed to be relevant regardless of being on active treatment or not. This is not appropriate. The ESC noted that the pivotal trial included prophylactic anti-emetics. Costs of supportive therapies (e.g. anti-emetics), disease monitoring and follow-up are likely to be higher in the romidepsin arm so excluding them favours romidepsin. Treatment with romidepsin requires clinical monitoring in order to diagnose and treat potential adverse events, make timely dose adjustments and evaluate treatment response. Such monitoring includes clinical consultations and diagnostic tests. Furthermore, after treatment, patients who received romidepsin were assumed to live substantially longer than patients in the comparator arm. During these additional life years, patients are likely to accrue additional health care costs. The failure to include any costs of concomitant therapies or disease monitoring (for romidepsin) or the costs of active therapies/best supportive care (for the comparator) introduced considerable uncertainty to the model. Excluding these costs resulted in biases in both directions, so the overall effect is unclear. The PBAC considered that this was a fundamental source of uncertainty in the economic analysis.
- 6.28 Table 6 provides a summary of the key drivers of the model.

Table 6: Key drivers of the model

Description	Method/Value	Impact
Survival times	Obtained from Australian registry data; PFS 32.8 months, OS 46.4 months in responders, PFS 3.0 months, OS 3.7 months in non-responders	High, favours romidepsin
Response rate	Obtained from Study 0002; 25.4% response; 0% for comparator.	High, high response rate favours romidepsin
Treatment duration	Obtained from Study 0002; 5.6 cycles	High, favours romidepsin
Number of vials per dose	Derived from BSA in Study 0002; mean 3 vials	High, favours romidepsin

Source: compiled during the evaluation

- 6.28 Treatment duration is likely to be dependent on response in the PBS population and the frequency of response assessment. In Study 0002, evaluation of treatment response was performed every two months. The submission did not propose a frequency of monitoring for progressive disease. The proposed listing for romidepsin did not include a maximum number of repeats.
- 6.29 Table 7 provides the results of the economic evaluation.

Table 7: Results of the economic evaluation

Component	Romidepsin	No active treatment	Increment
Costs	\$██████	\$0	\$██████
Lys	1.0957	0.2986	0.7971
QALYs	0.8645	0.2389	0.6256
Incremental cost per LY gained			\$██████
Incremental cost per QALY gained			\$██████^a

Source: Table 3, p 4 of attachment 1 ("Pricing, cost-effectiveness and budget impact of romidepsin for PTCL").

Abbreviations: LY, life years; QALYs, quality-adjusted life years.

^a Corrected value (as per section D.6 of the Commentary) = \$██████.

- 6.30 When correcting the base case analysis to include fees (mean drug cost per patient = \$██████) and a rounding error in the calculation of the number of vials per patient, the ICER was \$105,000 - \$200,000 instead of \$105,000 - \$200,000 per QALY gained.
- 6.31 Univariate sensitivity analyses indicate that the model is most sensitive to the source of survival times (see Table 8). When using PFS and OS based on Study 0002 instead of the registry data, this increased the ICER from \$105,000 - \$200,000 to more than \$200,000 per QALY gained. Using survival times from Study 0002 may be more appropriate than using survival times from the Australian registry since response was also obtained from Study 0002. It therefore prevents the need to define response based on TTNT, which likely introduced considerable bias in the base case economic evaluation. Furthermore, the use of Study 0002 as a source of survival data allows survival to be reported for the different response categories (CR, PR, SD, PD), rather than responders versus non-responders only.

- 6.32 The model is sensitive to a change in the response rate; using the upper and lower confidence interval of the response rate in Study 0002 changed the ICER from \$105,000 - \$200,000 to \$105,000 - \$200,000 (lower response rate) and \$75,000 - \$105,000 (higher response rate) per QALY gained. The confidence interval around the response rate is relatively wide due to the small patient numbers.
- 6.33 The model is sensitive to treatment duration. Using the mean number of treatment cycles from Piekarz 2011 (7.9 compared with 5.59 in Study 0002) resulted in a substantial increase of the ICER from \$105,000 - \$200,000 to \$105,000 - \$200,000 per QALY gained. In this sensitivity analysis, response was assumed to be unchanged since the median time to response in both studies was 1.8 months (most patients had responded before the mean number of cycles was reached).

Table 8: Results of selected univariate sensitivity analyses

Univariate analyses	Incremental costs	Incremental QALY	Incremental cost-effectiveness	Incremental cost-effectiveness corrected during the evaluation (include fees, mean drug cost per patient = \$ ██████, and mean 51.32 vials per patient)
Base case	\$ ██████	0.6256	\$ ██████	\$ ██████
Response rate 17.9% instead of 25.4% ^a	\$ ██████	0.4411	\$ ██████	\$ ██████
Response rate 32.0% instead of 25.4% ^a	\$ ██████	1.0048	\$ ██████	\$ ██████
OS 41.8 instead of 46.4 months ^b	\$ ██████	0.5720	\$ ██████	\$ ██████
OS 51.0 instead of 46.4 months ^b	\$ ██████	0.6782	\$ ██████	\$ ██████
PFS and OS based on Study 0002 (Coiffier et al. 2014) instead of the Australian registry	\$ ██████	0.2734	\$ ██████	\$ ██████
Mean number of cycles per patient of 7.9 instead of 5.6 (calculated during the evaluation) ^c	\$ ██████	0.6256	\$ ██████	\$ ██████

Source: Table 4, pp 4-5 of attachment 1 ("Pricing, cost-effectiveness and budget impact of romidepsin for PTCL").

Abbreviations: AE, adverse event; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALY, quality-adjusted life years.

^a Lower and upper confidence interval around response rate according to Coiffier et al 2012 (Study 0002) (33/130=25.4% [95%CI: 17.9%, 32.9%])

^b ±10% around overall survival with romidepsin based on the PeterMac/St Vincent's Hospital PTCL Patients Registry data

^c As obtained from Piekarz 2011 instead of Study 0002.

- 6.34 The PBAC considered that the modelled economic assessment was fundamentally flawed and precluded any decision on cost-effectiveness. Within the limits of

interpretation of the economic model provided, the PBAC considered that a substantial reduction in price was likely to be required to establish cost-effectiveness.

Drug cost/patient/course: \$ [REDACTED].

6.35 The drug cost per patient (with BSA 1.84 m²) is \$ [REDACTED] per dose and \$ [REDACTED] per cycle (3 doses per cycle). On average, patients received 5.59 treatment cycles in Study 0002.

Estimated PBS usage & financial implications

6.36 The submission adopted an epidemiological approach based on non-Hodgkin's lymphoma incidence projections from the Australian Institute of Health and Welfare (19/100,000), the proportion of PTCL patients estimated by Lymphoma Australia (7%), a relapse percentage of 70% (published review, Zinzani et al. 2016a), and the assumption that [REDACTED]% of patients with relapsed/refractory PTCL will use romidepsin on the PBS. Table 9 provides the resulting financial estimates.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Vials ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS/MBS determined during the evaluation ^c	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 58, Table 59 and Table 60, pp 159-160 of the submission.

^a The submission did not consider the number of scripts but the number of vials (10 mg). The average patient was estimated to use 3.05 vials per dose and 3 doses per cycle.

^b The submission calculated the net cost of romidepsin as \$ [REDACTED] (DPMQ per vial (\$ [REDACTED]) minus co-payment (\$ [REDACTED])).

^c This includes fees, 1 co-payment per script and 51.32 vials romidepsin per patient.

6.36 There is the potential for the net cost/year for the PBS to be lower than the estimate in the submission given that:

- The uptake in eligible patients is likely to be lower than [REDACTED]%. If a lower and staggered uptake is assumed (increasing from [REDACTED]% in year 1 to [REDACTED]% in year 4), total 5-year cost to the PBS is \$30 - \$60 million instead of \$60 - \$100 million

- (using corrected values).
- The dose per patient may be overestimated due to not taking into account dose adjustments.
 - The submission did not consider the treatments given to patients that would be substituted if romidepsin was listed on the PBS.
- 6.37 There is also potential for the net cost/year for the PBS to be higher than the estimate in the submission given that:
- The mean treatment duration may be longer than 5.6 cycles dependent on the frequency of response evaluation and if response is the same as in Study 0002.
 - Costs of prophylactic and supportive treatments have not been included in the financial forecasts.
- 6.38 The estimates will be higher than those included in the submission due to the correction of three errors:
- In the calculation of the number of vials (51.09 instead of 51.32).
 - The “DPMQ” used in the submission was the fixed ex-manufacturer price per vial, excluding fees.
 - The submission assumed one patient co-payment per vial instead of per original prescription.
- 6.39 Overall, the direction of bias in the estimates is unknown.
- 6.40 Based on the information provided in the evaluation the drug costs are likely to exceed \$10 million/year. At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 - \$20 million per year.

Financial Management

- 6.41 The submission requested a Special Pricing Arrangement with a published list price of \$██████ and an effective price of \$██████, representing a ███% discount. This was confirmed by Celgene Pty Ltd in a letter of support.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the Section 100 Authority Required listing of romidepsin for the treatment of peripheral T-cell lymphoma (PTCL), as the clinical data and economic analysis presented did not provide a basis for the PBAC to assess its comparative clinical effectiveness and cost-effectiveness. The PBAC considered that the submission’s approach to estimating cost-effectiveness was fundamentally flawed and could not provide sufficient certainty for decision making, and that this was unacceptable in the context of the magnitude of the predicted additional expenditure.
- 7.2 In making this recommendation, the PBAC recognised the high and unmet clinical need for an additional or alternative effective therapy in a group of patients with advanced PTCL after the failure of prior systemic therapy. The PBAC also agreed

with ESC that romidepsin could be used as bridging therapy to transplantation, and that this may be an important use of this drug in Australian practice. The PBAC noted that the estimated eligible population was less than 10,000 patients per annum, and considered that a sizeable minority were likely to achieve a durable response to romidepsin.

- 7.3 The PBAC noted ESC's concerns regarding "no active therapy" being the nominated comparator but considered that if recommended for PBS listing, romidepsin would be used to displace, rather than replace currently available treatments, which vary widely in nature and applicability to individual cases. As such, the PBAC viewed that "no active therapy" could reasonably be considered a comparator. Regardless, the PBAC noted that no comparative analysis against either comparator was presented.
- 7.4 The PBAC considered the efficacy and safety data were difficult to assess in the absence of a comparative analysis, and agreed with the ESC's advice that in the absence of comparative data, the effectiveness and safety of the comparator arm would usually be informed by other types of data, for instance: historical controls, registry data, or other single arm studies. The PBAC noted the ESC's advice that that application to the TGA for registration of romidepsin included a comparison with historical controls, which was not provided in the PBAC submission. The PBAC would have welcomed an opportunity to assess this analysis, particularly as a means of establishing if current treatments offer meaningful benefit to patients and for giving context to the durable responses to romidepsin as seen in some PTCL patients.
- 7.5 The PBAC noted that the key clinical evidence presented in the resubmission constituted two single-arm phase II studies (Study 0002, n=130 and Piekarz 2011, n=47) of romidepsin in PTCL. From the evidence presented in the resubmission, the PBAC considered that the romidepsin induced a durable response in a sizeable minority of patients with advanced PTCL; however the magnitude of any benefit was uninterpretable due to the limited and biased nature of the data. Moreover, the PBAC remained concerned about the heterogeneity of the PTCL patient population and the lack of evidence of underlying biological characteristics to explain the observed responses. The PBAC was consequently uncertain as to the applicability of the trial results to the various PTCL subtypes.
- 7.6 In terms of drug harms, the PBAC noted that the adverse events reported were from patients with ECOG performance status ≤ 2 . Patients in the proposed PBS population could have a worse performance status, and therefore be at greater risk of toxicity. The PBAC considered that the claim of inferior safety compared with no active therapy was reasonable.
- 7.7 The PBAC noted that the submission provided a modelled cost-utility analysis, and further remarked that:
- Australian registry data, from patients who progressed or died within 6 months of receiving a HDAC inhibitor (thereby ensuring progression free survival in this arm of less than 6 months), was used to model the comparator arm. By contrast, responders were selected on the basis of a time to next treatment (TTNT) of greater than 6 months. The PBAC considered that these assumptions biased the survival rates in favour of romidepsin, and were not well justified. The PBAC recognised that the intent of the approach, as explained in the submission, PSCR and pre-PBAC response, was to model outcome in the absence of

- romidepsin, but like the ESC, considered that the model was severely flawed.
- Costs of concomitant therapies or disease monitoring (for romidepsin) or the costs of active therapies/best supportive care (for the comparator) were not included in the model; excluding these costs resulted in biases in both directions, so the overall effect was unclear. The PBAC considered that this was a fundamental source of uncertainty in the economic analysis.
 - The Australian registry data did not differentiate between the types of HDAC inhibitors contributing to survival. The results are therefore not specific to romidepsin in PTCL (n=18), but also include patients treated with vorinostat (n=4) and panobinostat (n=8) in PTCL. The PBAC considered that there was a high degree of uncertainty on whether survival observed following other HDAC inhibitor can be used as a proxy for romidepsin. The PBAC noted that the PTCL database results included 30 patients whilst the CTCL database results included 67 patients. Given that PTCL represents a broader population than CTCL, but the registry provided a smaller sample size, the PBAC questioned the overall relevance of the registry data for modelling the cost-effectiveness of treatment for PTCL. Rather, the PBAC considered that the registry data might be of greater relevance for assessing treatment in the context of CTCL.
- 7.8 The PBAC considered that the modelled economic assessment was fundamentally flawed and precluded any decision on cost-effectiveness. Within the limits of interpretation of the economic model provided, the PBAC considered that a substantial reduction in price was likely to be required to establish cost-effectiveness.
- 7.9 The PBAC noted the submission's request for a grandfathering arrangement for 20 patients receiving romidepsin through the sponsor's Expanded Access Program (EAP). The PBAC considered that in order to be eligible for treatment under a grandfathering arrangement, patients on the EAP would need to have met the initial criteria at the time of commencing romidepsin.
- 7.10 The PBAC considered that the patient numbers in the financial estimates should account for the patients from the sponsor's EAP who would qualify for PBS-subsidised treatment under a proposed grandfathering arrangement. The PBAC also noted that EAP numbers would need to be confirmed by the sponsor of the drug.
- 7.11 The PBAC would welcome a future submission with comparative data and a revised economic evaluation, prepared in accordance with the PBAC Guidelines.
- 7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.