7.01 ROMIDEPSIN
Powder for infusion 10mg, Istodax®, Celgene Pty Limited

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). The first submission was considered by PBAC in November 2016.

1.2 The listing is requested based on cost-effectiveness compared with no active treatment.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Relapsed or refractory peripheral T-cell lymphoma (PTCL) (following at least first-line chemotherapy).
Intervention	Romidepsin
Comparator	No active therapy
Outcomes	Overall survival
Clinical claim	Improved overall survival from the time of first line therapy for patients subsequently treated with romidepsin compared to those who are not.

Source: Table 1, p11 of the submission
PTCL = peripheral T-cell lymphoma
SF36 = short form 36; VAS = visual analogue scale;

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
ROMIDEPSIN 10 mg powder for injection and solvent for reconstitution	31	17	Istodax®	Celgene

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity	*Relapsed or refractory*
Condition:	Peripheral T-cell lymphoma
PBS Indication:	*Relapsed or refractory* peripheral T-cell lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have undergone appropriate prior front-line systemic therapy, AND ~~Patient must demonstrate relapsed or refractory disease,~~ AND The treatment must be the sole PBS-subsidised ~~systemic~~ 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) a histological diagnosis of relapsed or refractory peripheral T-cell lymphoma and; (ii) details of prior treatment including name(s) of drug(s) and date of most recent treatment cycle

Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must be a sole PBS-subsidised ~~systemic treatment with this drug~~ *therapy* for this condition.

2.2 The current resubmission proposed a lower effective ex-manufacturer price per vial ($[redacted]) compared to the November 2016 submission ($[redacted]).

2.3 The maximum amount and number of repeats were appropriate. However, the resubmission calculated the published DPMA based on a maximum dose of 31 mg rather than a maximum of four vials that will be required to achieve the dose of 31 mg (they did not calculate the effective DPMA). The published DPMAs for romidepsin were recalculated in the evaluation to be $[redacted] (public hospital; $[redacted] in the resubmission) and $[redacted] (private hospital; $[redacted] in the resubmission) using four vials and most recent dispensing fees.

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

3 Background

Registration status

3.1 Romidepsin was TGA registered on 7 August 2013 for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.

Previous PBAC consideration

3.2 Romidepsin for the treatment of relapsed or refractory PTCL has been considered by the PBAC on one previous occasion as a major submission in November 2016. A summary of outstanding matters of concern to the PBAC are presented in Table 2.

Table 2: Outstanding matters of concern from November 2016 submission

Component	Matter of concern	How the resubmission addresses it
Clinical evaluation	The PBAC considered the efficacy and safety data were difficult to assess in the absence of a comparative analysis. The PBAC noted the ESC's advice that the 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. (para 7.4, Nov 16 romidepsin PSD)	The resubmission presented a comparison with historical (external) control data set representing a treatment career without romidepsin (205 patients). This was the same external dataset as presented to the TGA.
	The PBAC noted the heterogeneity of the PTCL patient population and was consequently uncertain as to the applicability of the trial results to the various PTCL subtypes. (para 7.5, Nov 16 romidepsin PSD)	The resubmission presents some discussion of representation of the different PTCL subtypes in Section 2, and some results are presented according to subtype. Given the small numbers of patients, this issue is difficult to address.
Economic evaluation	The comparator arm was populated with 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). 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 (para 7.7, Nov 16 romidepsin PSD).	The resubmission model presents historical control data from three sources to represent a "standard care" arm compared to data in the romidepsin treatment arm (from key Study 0002)
	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. (para 6.20, Nov 16 romidepsin PSD).	The resubmission model draws survival directly from the KM curves resulting from each of the control and Study 0002 datasets and assumes a 35.4% PFS period in each arm (based on direct observation from Study 0002).
	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. (para 7.7, Nov 16 romidepsin PSD).	The resubmission model added monitoring and follow-up costs of $34.83 and $69.95 per cycle respectively. The model also included the cost of the anti-emetic ondansetron of 16 mg per day for 2 days post chemotherapy treatment (for 78.6% patients – Study 0002).
Financial impact	The PBAC noted there were a number of assumptions that meant the financial impact might have been either over or underestimated.	Changes to some assumptions

Source: November 2016 romidepsin Public Summary Document (PSD), Compiled during the evaluation
HDACi = histone deacetylase inhibitor; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; PTCL = peripheral T cell lymphoma; TTNT = time to next treatment; yr = year

3.3 The ESC noted that pralatrexate had been recommended for listing for the treatment of peripheral T-cell lymphoma at the November 2017 PBAC meeting.

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

4 Population and disease

4.1 Peripheral T-cell lymphoma (PTCL) develops from mature T-cells and accounts for approximately 10-15% of all Non-Hodgkin Lymphoma (NHL) cases. NHL are cancers of the lymphatic system with an incidence of about 19/100,000 (AIHW, 2014). Current 5-year OS rate for patients with PTCL following a first relapse on conventional dose chemotherapy is 10-30% (Vose et al, 2008; Mak et al, 2013; Dreyling et al, 2013). In the absence of haematopoietic stem cell transplantation, treatment of relapsed or refractory PTCLs is usually palliative. Median survival in these patients is 5.5 months with survival only marginally improved in patients treated with chemotherapy after first relapse (Mak et al, 2013).

4.2 Romidepsin was proposed for the treatment of relapsed or refractory PTCL.

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

5 Comparator

5.1 The resubmission nominated "no active therapy" as the main comparator. This was previously accepted as appropriate by the PBAC (paragraph 7.3, November 2016 romidepsin Public Summary Document).

5.2 A submission for pralatrexate in PTCL was considered at the November 2017 PBAC meeting. Given the paucity of information available in PTCL, the ESC agreed that a comparison with pralatrexate as a possible 'near market' comparator was likely to provide some additional context for PBAC's consideration of romidepsin.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from one individual (1), via the Consumer Comments facility on the PBS website, noting the importance of access to medicines for patients.

Clinical evidence presented in the resubmission

6.3 The November 2016 submission presented a non-comparative analysis using data from Study GPI-06-0002 (hereafter referred to as Study 0002) and a separate phase II trial (Piekarz et al, 2011) to inform the efficacy and safety of romidepsin. No data for the comparative efficacy and safety of romidepsin over a "no active therapy" was presented in the previous submission. An updated literature search failed to identify any new comparative data for inclusion in the resubmission.

6.4 In the romidepsin Public Summary Document (PSD) from the November 2016 PBAC meeting, the committee noted that the submission 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".

6.5 The resubmission stated (p17) that the analysis referred to in the November 2016 PSD was a comparison of overall survival of PTCL patients given a "treatment career" which includes romidepsin compared to a treatment career which does not include romidepsin, and clarifies that, in the continued absence of comparative studies, "the intention of Section 2 (of the submission) is to present the same external control data comparison as was presented to the TGA in order to support the positive risk benefit ratio claimed for romidepsin in the previous submission." Based on the available information, the TGA consideration appears to have used the outcome of 'response', rather than overall survival, which is the outcome used in the resubmission. It is unclear whether the TGA considered overall survival, and also whether the 'treatment career' approach was presented to the TGA.

6.6 The resubmission was based on one phase II study (0002) and individual patient data sourced from three international databases:

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Treatment career with romidepsin		
Study 0002	Coiffier B, Pro B, 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; 30: 631-6.
	Coiffier, B., Pro, B., et al. "Romidepsin induces durable responses in patients with peripheral t-cell lymphoma: GPI-06-0002 study update."	Blood, 2012; 120 (21).
	Coiffier B, Pro B, 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."	Oral presentation at 53rd ASH Annual Meeting Dec 10-13, 2011. Blood 2011; 118 (21)
	Coiffier B, Pro B, 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."	Blood (ASH Annual Meeting Abstracts) 116: Abstract 114.Blood 2010; 116 (21).
	Coiffier B, Pro B, Prince HM et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses.	Journal of Hematology & Oncology 2014, 7:11.
	Foss F, Horwitz S, Pro B 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.	Journal of Hematology & Oncology 2016; 9:22.
	Foss F, Pro B, Prince HM, et al. Responses to romidepsin by line of therapy in patients with relapsed or refractory peripheral T-cell lymphoma.	Cancer Medicine 2017; 6(1):36–44.
Treatment career without romidepsin		
Historical control	Individual patient data 3 overseas databases (combined) 1986 – 2010	October 2013 Celgene Istodax® (romidepsin) – Istodax Historical Comparison report.

Source: Table 6, pp10-11 of the resubmission.

<u>Treatment career with romidepsin (Study 0002)</u>

6.7 The treatment career with romidepsin arm was based on Study 0002, which was a prospective single-arm, open-label phase II trial (N = 130), and was one of two key trials reported in the November 2016 submission. The other, Piekarz et al, (2011), was not included in the resubmission as the study was small and did not report on overall survival. This was appropriate.

6.8 Although Study 0002 was presented to the PBAC in the November 2016 submission and was evaluated in full at that time, data were used differently in the resubmission and this had not been presented previously. The resubmission presented a naïve comparison of "treatment career with romidepsin" (based on data from Study 0002) versus "treatment career without romidepsin" (based on the historical cohorts presented to the TGA). This approach meant that the benefit outcome (overall survival) was measured from the start of first line therapy to death or censoring (rather than from initiation of treatment with romidepsin). This was estimated based on observed individual data from Study 0002. Start and stop dates for each line of

therapy were retrospectively captured when patients were enrolled in Study 0002, and these data were used for the start date of the first line therapy. The ESC agreed that there is likely to be some selection bias favouring the romidepsin arm of the comparison, given that patients had to have survived for long enough to receive romidepsin treatment.

Treatment career without romidepsin (historical control cohort)

6.9 The treatment career without romidepsin arm (Historical Control Cohort, N=205) was constructed using individual patient data from:

- Two academic hospitals in the US with high-volume haematology departments and expertise in peripheral T-cell lymphoma (N = [redacted]); and
- The Groupe d'Etude des Lymphomes d l'Adlute (GELA), a European cancer cooperative group (N = [redacted]).

6.10 Data for a total of 254 patients were obtained across the three sources used to inform the historical control cohort. Key eligibility and exclusion criteria for Study 0002 were applied to this group, and the 205 patients who met the inclusion criteria for Study 0002 were included in the historical control cohort.

6.11 The Public Summary Document for the July 2017 pralatrexate submission notes that the historical control cohort constructed for that submission included patients from an Australian dataset from the Peter MacCallum Institute. This database is referred to in the romidepsin submission, however it was not included in the comparator arm of the clinical comparison.

Comparability of Study 0002 and the historical control cohort

6.12 The key features of the studies presented by the resubmission are summarised in the table below.

Table 4: Key features of the included evidence, treatment career with romidepsin vs. treatment career without romidepsin – naïve comparison

Trial	N	Design/ median duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in economic evaluation
Treatment career with romidepsin						
Study 0002	130	MC, OL/27.8 months	High	R/R PTCL	Response rate, DOR, PFS, OS, toxicity	Yes (OS, PFS)
Treatment career without romidepsin						
Cooperative group	[redacted]	Historical database (1997 – 2008)/24.2 months	High	R/R PTCL	OS	Yes
Hospital group	[redacted]	Historical database (1986 – 2010)/18.5 months	High	R/R PTCL	OS	Yes

Source: compiled during the evaluation
MC = multi-centre; OL = open label; OS = overall survival; PTCL = peripheral T-cell lymphoma; R/R = relapsed/refractory

6.13 Due to the limited information available for the historical control cohort, it was not possible to fully assess the comparability of patients in the comparative analysis set.

6.14 The following issues contributed to the uncertainty around the level of heterogeneity between the comparison arms:

- Inclusion but not exclusion criteria from Study 0002 were used to identify patients for the historical comparator cohort. This meant that patients in Study 0002 might have benefited from survival gains due to having fewer comorbidities compared with the historical control cohort;
- There may have been differences in the types of other treatments used in the two arms; and
- Patients in the romidepsin arm may have had less severe disease or a better prognosis, given that they had already survived long enough to receive treatment.

6.15 The Pre-Sub-Committee Response (PSCR, p1) acknowledged that there were potential confounders given the retrospective nature of the analysis, but states that "steps were taken to ensure unbiased selection of candidates for the external control arm", including that patients who died soon after completing a line of treatment "were generally not accepted for the external control dataset."

6.16 The ESC acknowledged the information provided in the PSCR, but considered that, overall, the comparability of the datasets remained uncertain, and that this was a key issue in accepting the reliability of the comparison presented in the submission.

Comparative effectiveness

Comparison with historical control cohort – overall survival

6.17 The effectiveness outcome presented in the resubmission was overall survival.

6.18 As noted above, the resubmission presented the overall survival results for Study 0002 taking a 'treatment career' approach, meaning that overall survival was measured from start of first-line therapy through to death or censoring. Given the uncertainty around the appropriateness of this approach, and the possible confounding of the benefit from other treatments, the overall survival results reported in Study 0002 for the ITT population and for the responder population (as presented in the November 2016 submission) were also presented in the results table, to provide some additional context to the PBAC around the impact of the treatment career approach on the survival estimate.

6.19 The overall survival for treatment career with romidepsin was 34.9 months (95% confidence interval (CI): 28.6 to 65.4) compared to [redacted] months (95% CI: [redacted] to [redacted]) in the historical control arm.

Table 5: OS results from study 0002 and the historical control cohorts

	Treatment career with romidepsin	Treatment career without romidepsin	Romidepsin only ITT	Romidepsin only Objective responder[a]
	Study 0002 (adjusted by resubmission)	Historical Control Cohort	Study 0002 (Coiffier 2014)	Study 0002 (Coiffier 2014)
N	130	[redacted]	130	130
Events, n (%)	76 (58.55%)	[redacted]	NR	33
Median OS, months (95% CI)	34.9 (28.6, 65.4)	[redacted]	11.3 (8.3, 22.1)	30 (2.0, 49.5)
Median follow-up, months (95% CI)	27.80 (3.8,153.8)	[redacted]	22.3 (NR, NR)	22.3 (NR, NR)

Source: Table 15, p22 and Table 14.2.2.4, p129 of Appendix A of the resubmission, and Coiffier 2014
CI = confidence interval; n/N = number; OS = overall survival
[a] Objective responder was a patient that obtained a confirmed/unconfirmed complete response or a partial response in Study 0002. This was the key outcome used in the November 2016 submission

6.20 Figure 1 presents the Kaplan-Meier curves of overall survival, for the comparative analysis of treatment career with romidepsin compared to the historical control cohort.

Figure 1: Kaplan-Meier OS curves for the external control dataset and treatment career with romidepsin (based on Study 0002)

[redacted]

Source: Figure 2, p21 of the resubmission
CI = confidence interval; OS = overall survival

6.21 No indirect comparative statistical analysis was conducted. This was appropriate, as there was considerable heterogeneity between the two data sources.

6.22 The OS difference may have been overestimated in favour of romidepsin as:

- In Study 0002 the exclusion criteria were comprehensive and excluded a number of comorbidities. All patients that met the inclusion criteria (though not necessarily the exclusion criteria) in the historical control cohort were enrolled.

This benefits romidepsin as patients would have worse comorbidities in the historical control cohort;

- The OS in Study 0002 was calculated so that patients were accumulating survival benefit prior to been treated with romidepsin. This would favour romidepsin as patients had to be alive for a considerable time after a previous line of therapy to receive romidepsin. In the historical control cohort, patients that died soon after a line of treatment were included in the analysis; and
- Study 0002 was conducted for a period of 3.5 years, with survival data collected both retrospectively and prospectively. The survival curve presented in the submission suggests that 23.6% of Study 0002 patients were still alive. This means that patients could have survived PTCL for up to 6.5 years prior entering Study 0002 and receiving romidepsin. In this case patients could have accrued the majority of their survival unrelated to romidepsin therapy.

Comparison with pralatrexate

6.23 The historical comparison document included at Appendix A of the resubmission presented a review of the efficacy results in Study 0002 and the pralatrexate study (PROPEL). PROPEL was an open label, non-randomised, single arm study of 109 patients with relapsed or refractory peripheral T-cell lymphoma. PROPEL was determined to have a high risk of bias, primarily due to the risk of confounding of results due to the absence of randomisation, the heterogeneity of the population and the absence of blinding. The PROPEL study had previously been presented to the PBAC in their considerations of submissions for the listing of pralatrexate for PTCL (paragraph 6.6, pralatrexate PSD, July 2017)

6.24 Table 6 presents the naïve comparison of romidepsin compared to pralatrexate from Appendix A of the resubmission.

Table 6: Comparison of romidepsin and pralatrexate based on independent panel assessment

	Romidepsin	Pralatrexate
	Study 0002	PROPEL
Efficacy Endpoint	(N = 130)	(N = 109)
Best Response Category ORR (95% CI)	25% (18, 34)	29% (21, 39)
CR	15%	11%
PR	11%	18%
SD	25%	19%
PD	49%	52%
Duration of Response (Months) Median (95% CI)	16.6 (11.6, NE)	10.1 (3.4, NE)
PFS (Months) Median (95% CI)	3.5 (2.5, 5.8)	3.5 (1.7, 4.8)
OS from Enrolment (Months) Median (95% CI)	11.3 (8.3, 22.1)	14.5 (10.6, 22.5)

Source: Table 23, p21 of Appendix A of the resubmission (Istodax Historical Comparison.pdf)
CI = confidence interval; CR = complete response; N = number, NE = not estimable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = Stable Disease

Comparative harms

6.25 The resubmission did not present comparative harms data from the included studies and no comparative safety data were available from either the previous submission or

the attached documents. This was appropriate, as there was considerable heterogeneity between the two studies and adverse event data were limited in the Historical Control Cohort.

6.26 All safety data originated from non-randomised, single arm, open-label studies. In Study 0002, the most frequent grade ≥3 adverse events were thrombocytopenia, neutropenia, and infections. Other frequent adverse events (which were seldom grade 3 or 4) included nausea, vomiting, asthenia/fatigue and diarrhoea.

6.27 The resubmission presented an extended assessment of comparative safety that included studies of chemotherapies in patients with non-Hodgkin lymphoma (NHL), but not specifically PTCL patients. Overall, the resubmission concluded that romidepsin had a relatively mild comparative safety profile to other chemotherapies. Given the presented evidence and the heterogeneous nature of the studies, it was not possible to estimate the true difference in safety between romidepsin and chemotherapy.

Benefits and harms

6.28 A summary of the comparative benefits of treatment career with romidepsin versus treatment career without romidepsin based on a naïve comparison is presented in Table 5 (in the overall survival section, above).

6.29 The extent of comparative benefit associated with romidepsin remains uncertain due to the nature of the evidence provided.

Interpretation of clinical evidence

6.30 The resubmission concluded that:

- A treatment career that includes romidepsin is superior to a treatment career that does not include romidepsin in terms of overall survival
- A treatment career that includes romidepsin is marginally inferior to a treatment career that does not include romidepsin in terms of safety.

6.31 The therapeutic conclusion presented in the submission is not strongly supported by the evidence presented in Section 2 of the submission. Although the evidence provided suggests an improvement in overall survival compared to no active treatment, the magnitude of any benefit remains unclear given:

- The claim was based on a naïve comparison of studies with high risk of bias;
- The comparison is likely to be impacted by survival bias; and
- The median overall survival of treatment career with romidepsin (34.9 months; 95% CI: 28.6, 65.4) was not different to treatment career without romidepsin ([redacted] months; 95% CI: [redacted], [redacted]) based on an overlap of confidence intervals.

6.32 The PBAC was satisfied that the claim of superior comparative effectiveness was likely to be reasonable, but considered that the magnitude of benefit remained uncertain.

6.33 The PBAC considered that the claim of inferior comparative safety was reasonable.

6.34 Whilst the results of the pralatrexate study PROPEL were included in an appendix to the submission, a formal clinical claim against pralatrexate was not provided. Based on the naïve comparison of efficacy endpoints between romidepsin and pralatrexate, the

sponsor's pre-PBAC response (p4) stated that the "romidepsin may be non-inferior to pralatrexate."

6.35 Based on the naïve comparison of romidepsin and pralatrexate, the PBAC considered that the efficacy and safety of these products were likely to be comparable.

Economic analysis

6.36 The resubmission presented a simple cost-utility analysis that compared the costs and QALYs generated from romidepsin (treatment arm) and "no active treatment" (control). The model was trial-based, using only raw survival data from the post hoc "treatment career with romidepsin" analysis from Study 0002 and the historical control cohort.

6.37 The model in the resubmission was substantially different from that presented in the November 2016 submission as:

- OS was determined directly from 10-year observed data in the key Study 0002 and a historical control dataset;
- It was assumed that progression free survival (PFS) was 35.4% of overall survival (OS) with the remainder of OS spent in progressive disease (PD), based on data from Study 0002;
- The number of doses, number of vials per dose, and proportion of adverse events was updated;
- Costs for concomitant medication, a hospital preparation fee, and monitoring were added; and
- Costs of romidepsin, drug administration, and adverse events were updated.

6.38 Table 7 provides a summary of the model structure.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case based on 10 year observed data in the key trial and historical control dataset
Outcomes	LYG and QALYs
Methods used to generate results	Trial-based; area under the curve for 10-year survival data in patients with a treatment career including romidepsin, or without romidepsin (control)
Health states	1) Alive 2) Dead
Utilities	Trial based; patients with relapsed/refractory Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma Swinburn (2015) Identical utilities were applied to each arm based on the proportion of time a patient spent in progression free survival and progressed disease from Study 0002.
Cycle length	Not modelled as LY and QALYs derived directly from observed KM data (monitoring costed following a 28 days cycle)
Transition probabilities	Not modelled (35.4% of OS spent in PFS)

Source: Table 25, p47 of the submission
KM = Kaplan-Meier; LY = life year; LYG = life years gained; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALYs = quality adjusted life years

6.39 A number of issues were identified in the new economic model including:

- The utility values applied in the model appeared unrealistically high (0.83 for stable disease and 0.67 for progressed disease), which maximised the QALY gain from increased survival;
- The model may have been oversimplified because:
  - Only two health states were considered: alive or dead;
  - Possibility of continuing romidepsin treatment beyond the 15.5 doses (i.e. a single course of treatment) was not modelled;
  - The model did not take into account different treatments, including stem cell transplant;
  - All patients in both treatment arms are assumed to spend 35.4% of their OS in PFS. This proportion is derived from the observation that for all patients in Study 0002 where the median PFS and OS were 4 months and 11.3 months respectively, and is used as a basis for the weighting of utilities in the model;
  - Cost of hospitalisation due to an adverse event was considered a one-time cost; and
  - All costs in the model were up front costs and were not modelled by time or response.
- The comparative efficacy and safety of romidepsin compared to no active therapy was uncertain; and
- The incremental difference in OS between the two treatment arms may be overestimated as it was based on a clinical comparison that may have favoured romidepsin.

6.40 The key drivers of the model are summarised in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
OS	AUC from 10-year survival data for both treatment arms Romidepsin treatment arm: Prospective data collection during Study 0002 period, retrospective for period prior to Study 0002 period Control treatment arm: Retrospective data only	High, favours romidepsin
Cost of drug treatment in both treatment arms	Model includes cost of romidepsin, administration, adverse events, concomitant medications, and monitoring Model assumes zero cost of comparator treatment (i.e. no treatment). Cost of monitoring only	moderate, favours comparator
Post progression treatment use	No post-progression costs were included	Uncertain, likely favour romidepsin
Cycles of romidepsin	Model assumes an average of 5.59 cycles based on direct observation from addendum to Study 0002 (an extended follow-up of Study 0002) A smaller study (Piekartz 2014) reported an average number of cycles of 7.9.	moderate, favours romidepsin
Utility values	Health state utility for patients in PD state assumed to accrue utility value of 0.67 (SD of NHL patients in Swinburn 2015)	High, favours romidepsin

Source: compiled during the evaluation
AUC = area under the curve; NHL = non-Hodgkin's lymphoma; OS = overall survival; PD = progressive disease; SD = stable disease

6.41 Table 9 presents a summary of the results of the economic evaluation.

Table 9: Results of the economic evaluation

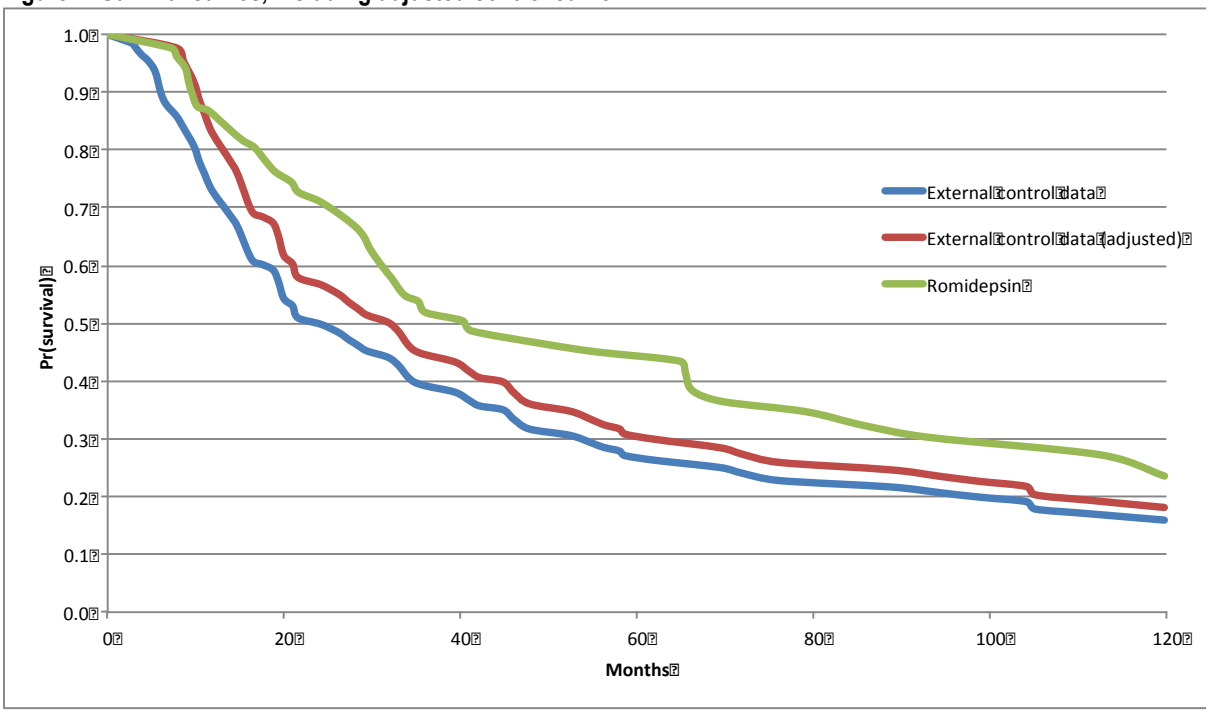
Component	Romidepsin	Comparator – No active therapy	Increment
Costs	$[redacted]	$[redacted]	$[redacted]
QALY	3.03	2.30	0.73
Incremental cost/extra QALY gained			**$**[redacted]

Source: Table 38, p59 of the submission
AE = adverse event; NA = not applicable to the model; QALY = quality adjusted life year

6.42 The resulting ICER in the model for the resubmission ($45,000 - $75,000 per QALY) is significantly lower than in the November 2016 submission ($105,000 - $200,000). This was primarily due to the decreased price of romidepsin and the higher incremental OS obtained using 10-year survival data from each treatment arm.

6.43 In order to estimate the impact of the survival bias described above (paragraph 6.8) on the estimate of cost effectiveness, the ESC performed a crude adjustment to the historical control data, whereby any patients who died in the control cohort before the first death in the romidepsin cohort (at approximately 7 months) were excluded from the analysis. This adjustment allowed for potential differences in responses to first-line therapy, which should not be present as eligibility criteria included completion of first-line therapy. The resulting survival curves are shown below.

Figure 2: Survival curves, including adjusted control curve



Source: Generated by ESC, as described in paragraph 6.43 above

6.44 The resubmission presented univariate sensitivity analyses. The key sensitivity analyses conducted by the resubmission, during evaluation, and by ESC are presented below.

Table 10: Results of the key sensitivity analyses

	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
Base case	$[redacted]	0.73	$[redacted]
Univariate analyses			
PFS as a proportion of OS (base case 35%)			
0%	$[redacted]	0.68	$[redacted]
50%	$[redacted]	0.76	$[redacted]
Utility values for health state PD (base case 0.67)			
0.32 value for PD in Swinburn 2016	$[redacted]	0.51	$[redacted]
0.746 value for SD (Kang 2015)[a]	$[redacted]	0.79	$[redacted]
0.567 value for PD (Kang 2015)	$[redacted]	0.67	$[redacted]
Reduction in incremental OS (1.01 years in base case)			
0.8 years as in the November 2016 model (Australian population – HDACi treated)	$[redacted]	0.58	$[redacted]
OS in Historical Control treatment arm (3.37 in base case)			
3.534 (baseline adjustment)	$[redacted]	0.46	$[redacted]
Number of cycles per patient (base case 5.59 cycles)			
7.9 cycles (Piekartz 2011)[b]	$[redacted]	0.73	$[redacted]
Multivariate analyses			
0.75 used for PF (stable disease in Kang 2015) 0.57 used for PD (progressed disease in Kang 2015) Baseline OS adjusted for control group (only those surviving >7 months)	$[redacted]	0.40	$[redacted]
0.78 used for PF (Unweighted mean* of Complete response, Partial response, & Stable disease Swinburn et al (2015)) 0.32 used for PD (progressed disease in Swinburn et al 2015) Baseline OS adjusted for control group (only those surviving >7 months)	$[redacted]	0.31	$[redacted]

Source: Table 41, p61 of the submission, and calculated during the evaluation
AE = adverse event; DPMQ = dispensed price maximum quantity; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; PD = progressive disease; PFS = progression free survival; SD = stable disease
*the use of an unweighted mean overestimates the actual benefit in this population
[a] health state utilities for relapsed or refractory peripheral T-cell lymphoma
[b] input 23.4 doses per patient and 69.68 vials per patient to cost calculations (Section 3 economic evaluation.xlsx)

6.45 The model is most sensitive to cost of romidepsin, the number of cycles of romidepsin and the utility values applied to the time spent in progressed disease.

6.46 A multivariate sensitivity analysis applying the adjusted control survival data and lower utilities (0.78 and 0.32 for stable and progressed disease respectively, from Swinburn et al 2015) increased the ICER from $45,000 - $75,000 to $105,000 - $200,000.

Drug cost/patient/course: $[redacted]

6.47 The total cost of romidepsin treatment was calculated to be $[redacted] (assuming a cost of per vial of $[redacted]; 45.62 vials per patient; 15.5 doses per patient; and $83.22 hospital preparation fee per dose). The total cost of comparator treatment was $[redacted] (assuming cost of monitoring and follow-up only for the comparator).

6.48 In the November 2016 submission, the cost of romidepsin was calculated to be $[redacted] per patient per course. No costs were attributed to the comparator (no active treatment).

Estimated PBS usage & financial implications

6.49 This submission was not considered by DUSC.

6.50 The resubmission used an epidemiological approach to determine the likely number of patients and costs associated with listing romidepsin on the PBS/RPBS. The method of calculation of the number of NHL patients per year was different to the previous submission. In the November 2016 submission, the incidence of NHL was determined by applying an estimate of incidence of NHL of 19 per 100,000 to the projected population of Australia. The resubmission conducted a linear extrapolation of NHL incidence data (from 2008 to 2013) to estimate expected NHL incidence figures for 2018 to 2023.

6.51 Individual patient data were used to calculate the average use of romidepsin (updated from the Study 0002 Addendum). The cost of concomitant anti-emetic treatment (ondansetron only), a drug administration fee, and a hospital preparation fee were included in the estimates for romidepsin (No concomitant treatment was included in the November 2016 Submission). The costs of monitoring and follow-up were included in the estimates for romidepsin and no active therapy (not included in the November 2016 Submission). The cost per vial of romidepsin and the average co-payment per dose were updated for the romidepsin treatment arm. As in the November 2016 submission, no treatment costs were included in the comparator treatment arm (considered no active therapy).

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of romidepsin						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for ondansetron						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS[b]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 43, p65, Tables 45-47, pp67-69 of the submission
MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Assuming 15.5 doses per year as estimated by the submission
[b] Calculation error, the resubmission used $[redacted] per patient. The true value is $[redacted] per patient as discussed in Section 4.5.2, p69 of the resubmission. *Values recalculated to reflect this error.*

6.52 During evaluation there was an error identified in the calculation of the net cost to the MBS by applying an average cost per hospital admission of $[redacted] per patient instead of the true value of $[redacted] per patient.

6.53 The number of patients treated with romidepsin in the resubmission was higher than estimated in November 2016 submission. This was primarily due to the new approach to determining the number of incident NHL cases (linear extrapolation of five years of recorded AIHW NHL incidence data to estimate 2018 to 2023 figures).

6.54 The net cost to the PBS/RPBS in Year 6 was $10 - $20 million. This was slightly lower than the estimates provided in the previous submission due to the decrease in the cost of romidepsin.

6.55 There was uncertainty in the estimates of net cost to government:

- The uptake in eligible patients is likely to be lower than 96% (overestimate);
- The submission did not consider the treatments given to patients that would be substituted/displaced if romidepsin was listed on the PBS (underestimate);
- The cost of a co-payment for ondansetron was not included in the December 2017 resubmission (overestimate); and
- Treatment duration may be longer as it is likely frequency of response evaluation would be longer in practice (overestimate).

Financial management – risk sharing arrangements

6.56 The resubmission requested a Special Pricing Arrangement such that the published ex-manufacturer price per 10 mg vial of romidepsin is $[redacted]. The resubmission requested an effective ex-manufacture price of $[redacted], representing a [redacted]% discount on the published price.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation to list romidepsin for the treatment of PTCL. Accepting that there remained a clinical need for additional therapies in PTCL and that romidepsin provided a degree of clinical benefit in some patients, the PBAC considered that the most appropriate comparison was against pralatrexate, and therefore the decision was deferred to allow for further discussion with the sponsor around this comparison.

7.2 In making this decision, the PBAC acknowledged the request from the Sponsor, received while the committee was in session, for consideration of the submission to be deferred until the March 2018 meeting. The PBAC noted that this request was made to allow further discussions within Celgene and its parent Corporation about PBS subsidised access to romidepsin in Australia. However recognising the clinical need in this patient population, that the Committee had information before it for the consideration of romidepsin, and had invested considerable resources for the submission to be considered at the meeting, the PBAC decided at its own motion to proceed with its consideration of the submission.

7.3 As in their previous consideration of romidepsin, 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, and considered that this clinical need remained despite the recommendation for listing of pralatrexate in this patient population.

7.4 Although the PBAC accepted that "no active therapy" was the appropriate comparator at the time the submission was lodged, the PBAC considered that pralatrexate was now also an appropriate comparator, given that it had been recommended for the same patient population at the November 2017 PBAC meeting.

7.5 While the PBAC acknowledged that romidepsin is active and could significantly benefit a minority of patients with PTCL, the committee considered that its net average benefit across the spectrum of patients with PTCL is small, and that the cost is very high.

7.6 The PBAC considered that the estimated magnitude of clinical benefit was highly uncertain due to the absence of direct comparative data, and the low quality of the indirect treatment career data used for the comparison.

7.7 The PBAC noted the survival estimates calculated by the ESC, and considered that these gave an upper estimate of the survival curve for the historical cohort, and that the true curve was likely to sit somewhere between the submission and ESC estimates.

7.8 The PBAC considered that the economic model presented in the submission in relation to the cost utility claim over the "no active therapy" comparator introduced additional uncertainties, and did not provide a suitable basis for determining the cost effectiveness of romidepsin in the PBS context. In particular the PBAC's concerns with the model included the lead time bias associated with the treatment career approach, the simplicity of the model structure, the duration of romidepsin use assumed, and the utility values applied in the model.

7.9 The PBAC considered that the ICER generated by the cost utility analysis was likely to exceed $105,000 - $200,000/QALY, which was unacceptably high. Given the uncertainties inherent in the analysis, the PBAC considered that a substantial price reduction would be required for romidepsin to be considered cost-effective.

7.10 The PBAC noted that, based on the naïve comparison of romidepsin and pralatrexate prepared during evaluation, it might be reasonable to assume that the benefit and safety of these products was comparable. Given the recent listing of pralatrexate in this patient population, the PBAC considered that an alternative approach to determining the cost-effectiveness of romidepsin would be would be via a cost-minimisation analysis with pralatrexate as the comparator, and therefore deferred its decision to allow discussion with the applicant around comparison of these two products ahead of further consideration by the PBAC.

7.11 The PBAC noted a number of uncertainties around the estimated financial implications presented in the submission:

- the submission's estimate of less than 10,000 patients per annum was likely to be an overestimate;
- should romidepsin and pralatrexate both be available through the PBS sequential use was likely, and any future estimates of financial implications should account for this;
- average duration of use of romidepsin may have been underestimated, given there is a small proportion of patients where longer term use (up to several years) is likely.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Deferred

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.