5.07 ROMIDEPSIN, Powder for injection, 10 mg, ROMIDEPSIN-REACH®, Reach Pharmaceuticals Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 listing for romidepsin for the treatment of adult patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) following at least one prior systemic therapy.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus pralatrexate.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults with relapsed or refractory PTCL (including AITL, ALCL, PTCL-NOS) who have received ≥1 prior systemic therapy.
Intervention	Romidepsin, a histone deacetylase inhibitor, administered at 14 mg/m² intravenously (IV) on Days 1, 8 and 15 of a 28-day cycle, until disease progression or unacceptable toxicity.
Comparator	Pralatrexate 30 mg/m² administered IV once weekly for 6 weeks, followed by one week rest period (7-week treatment cycle). The cycle repeated until progression or toxicity.
Outcomes	Overall response rate, compete response/partial response rates, duration of response, overall survival.
Clinical claim	For the treatment of patients with relapsed or refractory PTCL who have received at least one prior systemic therapy, treatment with romidepsin compared to pralatrexate is associated with: • Non-inferior effectiveness and • Different, but non-inferior safety.

Source: Table ES.1 pp10-11 and Table 1-1, p23 of the submission.
PTCL = peripheral T-cell lymphoma; AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma not-otherwise-specified.

2 Background

Registration status

2.1 Romidepsin was registered in Australia in 2013 for the treatment of patients with PTCL who have received at least one prior systemic therapy. Romidepsin was marketed under the trade name Istodax® by Celgene until 2019, when Celgene was acquired by Bristol-Myers Squibb.

2.2 Romidepsin as the generic brand, ROMIDEPSIN-REACH® was registered by the TGA in 2022 for the same indication.

2.3 Romidepsin received accelerated approval for PTCL in patients who had received at least one prior systemic therapy by the Food and Drug Administration (FDA) in 2011, undertaking a confirmatory post-marketing trial (Bachy., et al[1]), which failed to show a statistically significant benefit in terms of complete response (CR) or progression free survival (PFS) in untreated patients with PTCL. Romidepsin was conditionally approved in Canada in 2013 for treatment of PTCL in patients previously treated with at least one systemic therapy. Approval was withdrawn by Health Canada in 2023 because the results of the confirmatory trial in patients with untreated PTCL were unfavourable.[2]

2.4 In 2013 the European Medicines Agency (EMA) refused marketing authorisation for romidepsin for the treatment of PTCL in previously treated patients, given that data supporting the use of romidepsin were from an uncontrolled study so that "it was not possible to conclude that the benefits of the medicine outweigh the risks".[3]

Previous PBAC consideration

2.5 The PBAC considered submissions for romidepsin powder for IV infusion 10 mg (Istodax®) for the treatment of R/R PTCL in November 2016 and December 2017.

2.6 The PBAC did not recommend the submission in November 2016. A resubmission was scheduled for the December 2017 meeting, but at the November 2017 meeting pralatrexate was recommended for listing for the same condition and the sponsor asked for consideration of romidepsin to be postponed "to allow further discussions within Celgene and its parent Corporation about PBS subsidised access to romidepsin in Australia" (Paragraph 7.2, Romidepsin Public Summary Document [PSD], December 2017 PBAC Meeting). The PBAC declined this request, and after consideration, deferred its decision:

- "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" (Paragraph 7.1, Romidepsin PSD, December 2017 PBAC Meeting).
- "The PBAC noted that, based on the naïve comparison of romidepsin and pralatrexate prepared during evaluation [using GLP-0002 for romidepsin and PROPEL for pralatrexate], it might be reasonable to assume that the benefit and safety of these

[1] Bachy E, Camus V, Thieblemont C, et al. Romidepsin plus CHOP versus CHOP in patients with previously untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA). *J Clin Oncol* 2022; 40:242-251.

[2] https://recalls-rappels.canada.ca/en/alert-recall/istodax-romidepsin-restricted-access-program Accessed 9 November 2025.

[3] https://www.ema.europa.eu/en/medicines/human/EPAR/istodax Accessed 9 November 2025.

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 via a cost-minimisation analysis with pralatrexate as the comparator…" (Paragraph 7.10, Romidepsin PSD, December 2017 PBAC Meeting).

- No subsequent resubmission was made.

2.7 The clinical evidence was similar to that in the prior submissions; however, this submission included a comparison between romidepsin and pralatrexate, that had not been previously considered.

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
ROMIDEPSIN	$5,219.43 public hospital $5,366.90 private hospital	40 mg	5
ROMIDEPSIN	$5,219.43 public hospital $5,366.90 private hospital	40 mg	8
Available brands			
ROMIDEPSIN-REACH (romidepsin 10 mg powder for injection vial and solvent for reconstitution vial)			

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system) ☒Authority Required - Electronic
Indication: Relapsed or refractory peripheral T-Cell lymphoma
Treatment Phase: Initial treatment
Clinical criteria:
Relapsed or chemotherapy refractory,
AND
Clinical criteria:
Patient must have undergone appropriate prior front-line curative intent chemotherapy.

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system) ☒Authority Required - Electronic
Indication: Relapsed or refractory peripheral T-Cell lymphoma
Treatment Phase: Continuing treatment
Clinical criteria:
The condition must be relapsed or chemotherapy refractory,
AND

Clinical criteria:
Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition

3.1 The submission requested an ex-manufacturer price of $1,282.05 per 10 mg vial.

3.2 The submission proposed restrictions for initiating and continuing treatment modelled on the current restrictions for pralatrexate, and a grandfather restriction for patients who have previously received non-PBS subsidised treatment.

3.3 The proposed restriction does not preclude sequential use of pralatrexate and romidepsin or concomitant use of romidepsin with pralatrexate or other agents. The PBAC noted in 2017 that sequential use of pralatrexate and romidepsin was likely, which would have important implications for the volume of use (Paragraph 7.11, Romidepsin PSD, December 2017 PBAC Meeting). Several studies of combination treatment including romidepsin have been reported.[4,5] The Pre-Sub-Committee Response (PSCR) stated that the sponsor was open to limiting PBS-subsidised use to single agent therapy, should this be required, and noted that the submission had not sought a restriction that allows concomitant use of romidepsin with pralatrexate or other agents. The ESC noted that trials of romidepsin in combination with azacitidine had reported good results[6] and that some clinicians had indicated that azacitidine will still be used in combination with romidepsin even if it is not PBS-subsidised. The ESC considered that it was reasonable to allow sequential use of romidepsin and pralatrexate in patients who were well enough to use another agent, and that combination use with self-funded azacitidine or with pralatrexate was both likely and reasonable.

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

4 Population and disease

4.1 The peripheral T-cell lymphomas are a heterogeneous group of neoplasms of mature T-cell or NK (natural killer) cell lineage. The PTCLs account for 10-15% of non-Hodgkin lymphomas; AIHW reported 5,945 cases of non-Hodgkin lymphoma in Australia in

[4] Amengual JE, Lichtenstein R, Lue J, et al. A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. *Blood* 2018; 131:397-407.
[5] Yun KRT, Jain S, Barta SK, et al. Phase II study of the novel antifolate agent pralatrexate in combination with the histone deacetylase inhibitor romidepsin for the treatment of patients with mature T-cell lymphoma. *Leukemia & Lymphoma* 2024; 65:736-745.
[6] Falchi L, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. *Blood* 2021; 137 (16):2161-2170.

2021. There is a slight male predominance (incidence 26.4 vs 20.0/100,000). The median age of patients with PTCL is about 60 years.

The principal sub-types of PTCL are:

- PTCL not-otherwise-specified (PTCL NOS), accounting for 20-40% of PTCL. PTCL NOS is a diagnosis of exclusion used when the lymphoma cells do not correspond to any of the currently defined specific sub-types.
- Angioimmunoblastic T-cell lymphoma (AITL), the most common specific sub-type of PTCL, accounting for about 20% of PTCL.
- Anaplastic large cell lymphoma (ALCL), sub-categorised as positive or negative for anaplastic lymphoma kinase (ALK) gene expression.
- Enteropathy-associated T-cell lymphoma (EATL), most commonly associated with coeliac disease.
- NK/T-cell lymphoma (NKTCL), closely associated with Epstein-Barr virus infection and most common in Asia.

4.2 The standard treatment of previously untreated patients with PTCL includes cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP), or brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone (BV-CHP) for CD30-positive cases. Patients with NKTCL are usually treated with chemo-radiotherapy regimens not including anthracyclines.

4.3 Patients who are refractory to first-line chemotherapy or who relapse after responding have a poor prognosis, with median overall survival about 6 months. The ESC noted that patients have few treatment options.

4.4 Australian consensus guidelines suggest that patients with R/R PTCL (other than ALCL and NKTCL) may be treated with second-line combination chemotherapy or one of the treatments listed under the heading of "novel agents". The guidelines note that registry data suggest that novel agents may be superior to combination chemotherapy and support their use as second-line and third-line treatment of transplant-eligible and for transplant-ineligible patients.[7] Treatment included as novel agents in the Australian guidelines are brentuximab vedotin for patients with CD-30 positive lymphomas other than ALCL, pralatrexate, cyclosporin, and romidepsin and combinations with it, including romidepsin + pralatrexate, romidepsin + azacitidine and romidepsin + lenalidomide.

[7] Han JX, Koh MJ, Boussi L et al. Global outcomes and prognosis for relapsed/refractory mature T-cell and NK-cell lymphomas: results from the PETAL consortium. *Blood Advances* 2025; 9:583-602.

4.5 The ESC noted R/R PTCL that treatment decisions should account for the stage of the disease when selecting therapy. The ESC stated that management may involve combination approaches including salvage chemotherapy, allograft transplantation and targeted agents to get the best treatment possible and improve outcomes based on the disease stage. The ESC considered that romidepsin may be used in 1) sequence for patients who are well enough to use another agent, 2) prior to pralatrexate in some patients, and 3) in combination with other agents such as pralatrexate or in combination with azacitidine in some patients (particularly those who are being considered for allograft).

4.6 The PBAC noted romidepsin is a preferred second line and subsequent treatment regimen for patients with PTCL-NOS, EATL, and AITL in the National Comprehensive Cancer Network Guidelines[8].

4.7 Romidepsin is a cyclic depsipeptide isolated from a soil microbe and is an inhibitor of histone deacetylase (HDAC). Acetylation and deacetylation of histones is an important mechanism modulating gene expression, with inhibition of histone deacetylase and thus increased acetylation broadly enhancing gene expression. The net effect in tumour cells is to promote cell cycle arrest and apoptosis.

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

5 Comparator

5.1 The nominated comparator was pralatrexate. The ESC considered that pralatrexate was the appropriate comparator.

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 input

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (17) and organisations (the Snowdome Foundation, Lymphoma Australia and Rare Cancers Australia) via the Office of Health Technology Assessment Consultation Hub. The inputs described PTCL as a rare, aggressive and therapeutically underserved malignancy, with poor response durability, high relapse rates, and few effective salvage options. The inputs described the poor prognosis for patients with

[8] NCCN Clinical Practice Guidelines in Oncology, T-Cell Lymphomas, Version 2.2026 – February 13, 2026

R/R PTCL, the anxiety caused by lack of access to affordable treatment options, and the potential for romidepsin to improve symptoms, reduce time spent in hospital and help patients remain independent and connected to their community. Health care professionals noted that response to romidepsin is quick, thus limiting long unnecessary use in non-responders. Safety was described as predictable and manageable. The input also stated that romidepsin can be used as a bridge to stem cell transplant in patients eligible for transplant. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical studies

6.3 The submission relied on published data from three studies, two with romidepsin and one with pralatrexate. All were prospectively collected case series (single arm, open-label trials), although some data in the main romidepsin trial was retrospective. All three studies were considered by PBAC when romidepsin and pralatrexate were considered in 2016 and 2017. These studies are listed in

6.4 Table **2**.

6.5 One study identified by the literature search in the submission (Maruyama et al., 2017) was considered to have been inappropriately excluded. This was NCT01456039, a Phase I/II open-label, single-arm study of romidepsin in Japanese patients with R/R PTCL and CTCL (N = 48 with PTCL).[9] Insufficient efficacy data were available to compare the results with the submitted trials, but adverse event data have been included herein.

6.6 The Peripheral T-cell Lymphoma (PETAL) consortium has recently published pooled data from ten international registries on 925 patients with R/R PTCL (68 from Australia) treated between 2010 and 2021 (Han et al., 2025). These data have been included herein, particularly with regard to prognostic factors in the included romidepsin and pralatrexate studies.

6.7 A further trial identified in the literature search but excluded, O'Connor et al., 2019 (the LUMIERE trial)[10] reported on patients and on outcomes for patients with PTCL who had R/R PTCL after 1 or more prior systemic therapies. Patients were randomised to alisertib (138 patients) or to investigators choice, which included pralatrexate[11] (80 patients), romidepsin[12] (24 patients) and gemcitabine (30 patients). Demographic

[9] Maruyama D, Tobinai K, Ogura M, et al. Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell lymphoma: a phase I/II and pharmacokinetics study**.** *Int J Hematol* 2017; 106:655-665.

[10] O'Connor OA, Özcan M, Jacobsen ED, et al: Lumiere Study Investigators. Randomized Phase III Study of Alisertib or Investigator's Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma. J Clin Oncol. 2019 Mar 10;37(8):613-623.

[11] 30 mg/m^2 once a week for 6 weeks of a 49-day cycle

[12] 14mg/m^2 on Days 1, 8 and 15 of a 28-day cycle

details and outcomes are reported in the trial for patients treated with pralatrexate and with romidepsin. The PBAC previously noted that "Limited analysis of data from the LUMIERE trial where both pralatrexate and romidepsin were included in a basket of comparators for an experimental drug indicates that romidepsin may have a substantially longer PFS [progression free survival] than observed for pralatrexate (8.0 vs 3.4 mths, respectively; O'Connor ASH 2015)" (Paragraph 6.32, Pralatrexate PSD, July 2017 PBAC meeting). The trial reported median PFS was 101 days for pralatrexate and 242 days for romidepsin. Maximum follow-up in the trial was 35 months.

6.8 The submission presented an unanchored comparison of the study results from the included studies. The submission stated that a formal indirect treatment comparison (ITC) with a common comparator was not possible because the studies were uncontrolled.

6.9 The submission stated that the unanchored comparison was "provided for context only to inform the economic framing (cost-minimisation scenarios)" and that it was "not designed to demonstrate superiority, equivalence, or non-inferiority".

Table 2: Studies and associated reports

Study ID	Publication title	Publication citation
Romidepsin		
NCT00426764 GPI-06-0002	Coiffier B, Pro B, Prince HM, 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; 30:631-636.
	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.	J Hematol Oncol 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 trial.	J Hematol Oncol 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 Med 2017; 6:36-44.
NCT00007345	Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma.	Blood 2011; 117:5827-5834.
NCT01456039	Maruyama D, Tobinai K, Ogura M, et al. Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell lymphoma: a phase I/II and pharmacokinetics study.	Int J Hematol 2017; 106:655-665.
Pralatrexate		
NCT00364923 PROPEL PDX-008	O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory Peripheral T-Cell Lymphoma: Results from the pivotal PROPEL study.	J Clin Oncol 2011; 29:1182-1189.

Source: Modified from Table 2-2, p44 of the submission.

6.10 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
GPI-06-002	130	Single arm OL; MC; 6 cycles then continue if benefit.	High	PTCL with no response to ≥1 previous systemic therapy.	CR + CRu (IWC) assessed by IRC.
Piekarz, 2011	47	Single arm OL; Simon 2-stage design, with ≥2/16 responders in stage 1 to proceed to stage 2.	High	In stage 1, PTCL NOS or cutaneous ALCL with ≤2 prior systemic therapies; in stage 2 any PTCL and any number of prior therapies.	CR + CRu or partial response (IWC).
Maruyama, 2017	48	Single arm OL: Phase I used dose-escalation to dose-limiting toxicity; then Phase II treatment at identified maximum dose (= 14 mg/m^2) until disease progression or withdrawal.	High	Age ≥20; PTCL with progressive disease after ≥1 prior systemic treatment; ECOG ≤2.	CR + CRu + partial responses (IWC) assessed by IRC.
PROPEL	111	Prospective single arm OL; MC; Simon 2-stage design with ≥4/35 in Stage 1 to proceed to Stage 2, with total enrolment 100 and treatment until progression or toxicity.	High	PTCL with no response to ≥1 prior therapy.	CR + CRu + partial responses (IWC) assessed by IRC.

Source: Constructed during the evaluation from published reports.
CR = complete response; CRu = unconfirmed complete response; IRC = independent review committee; IWC = International Workshop Criteria; MC = multi-centre; OL = open label; PTCL = peripheral T-cell lymphoma; PR = partial response; R/R refractory or relapsed; SC = single centre.

6.11 Complete responses were defined by International Workshop Criteria (IWC) (1999), based on a computed tomography (CT) scan; CR required disappearance of clinical disease and of laboratory abnormalities, and a longest transverse diameter of previously enlarged lymph nodes of 1.5 cm; an unconfirmed complete response (CRu) required a greater than 75% reduction of tumour size.[13] The studies reported complete responses and unconfirmed complete responses as a single outcome.

6.12 Complete inclusion and exclusion criteria are shown in

[13] Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999; 17:1244.

6.13 Table 4.

6.14 A notable difference among the studies was the requirement in the romidepsin studies to exclude patients for a wide range of cardiac abnormalities, for low potassium or magnesium levels, and for use of drugs inhibiting CYP3A4 or affecting the QT interval.

Table 4: Inclusion and exclusion criteria for the studies

	Romidepsin Studies			Pralatrexate Study
	GPI-06-002	**Piekarz, 2011**	**Maruyama, 2017**	**PROPEL**
Inclusion Criteria				
Disease	PTCL, any sub-type with measurable disease and R/R after at least one prior therapy.	Initially, PTCL NOS or cutaneous ALCL, later PTCL, any sub-type, with measurable disease and R/R after at least one prior therapy.	PTCL, any sub-type with measurable disease and R/R after at least one prior therapy.	PTCL, any sub-type with measurable disease and documented disease progression after at least one prior therapy.
Age (years)	≥18	≥18	≥20	≥18
Prior Therapies	≥1	Initially, ≤2 later ≥1	≥1	≥1
ECOG	0-2	0-2	0-2	0-2
Adequate haematological, hepatic and renal function	ANC ≥1x10^9/L, platelets ≥l00 10^9/L, bilirubin ≤1.5 x ULN, AST ≤3x ULN, creatinine ≤1.5 ULN.	ANC ≥1x10^9/L, platelets ≥l00 10^9/L, bilirubin ≤1.5 x ULN, AST ≤3x ULN, creatinine ≤1.5 ULN.	Hb ≥80 g/L; ANC ≥1x10^9/L, platelets ≥l00 10^9/L, bilirubin ≤2 x ULN, AST ≤2 x ULN, creatinine ≤2 x ULN.	ANC ≥1x10^9/L, platelets ≥l00 10^9/L, bilirubin ≤1.5 x ULN, AST ≤3x ULN, creatinine ≤1.5 ULN.
Exclusion Criteria				
Cardiac abnormalities	Any significant cardiac abnormality, including prolonged QT interval or recent MI; serum K <3.8mol/L or serum Mg <0.85 mmol/L unless corrected before enrolment.	Any significant cardiac abnormality, including prolonged QT interval or recent MI; serum K <3.8mol/L or serum Mg <0.85 mmol/L unless corrected before enrolment was added during the study.	Any significant cardiac abnormality, including prolonged QT interval or recent MI; serum K <LLN or serum Mg <LLN.	No exclusions.
CNS Involvement	Exclude	Exclude	Exclude	Exclude
Medications	CYP3A4 inhibitors or warfarin, medications affecting the QT interval.	CYP3A4 inhibitors or warfarin added as exclusion criteria during the study.	CYP3A4 inhibitors or warfarin, medications affecting the QT interval; rifampicin.	No medication exclusions
Therapies	Chemotherapy or immunotherapy within 4 weeks; prior allogeneic SCT.	Chemotherapy within 4 weeks, immunotherapy within 2 weeks.	Chemotherapy or immunotherapy within 22 days; prior allogeneic SCT.	Chemotherapy or radiotherapy within 4 weeks; prior allogeneic SCT; monoclonal antibody therapy allowed.

Source: Constructed during the evaluation from published papers

ALCL = anaplastic large cell lymphoma; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CNS = central nervous system; ECOG = Eastern co-operative oncology group performance status 0 = no restriction compared to pre-disease, 1 = restricted but able to do light or sedentary work, 2 =ambulatory and able to self-care but unable to work, active >50% of waking hours, 3 = limited self-care and >50% of waking hours in bed or chair, 4 = disabled, confined to bed or chair, 5 = death; Hb = haemoglobin; NOS = not otherwise specified; K = potassium; LLN = lower limit of normal; Mg = magnesium; PTCL = peripheral T-cell lymphoma; SCT = stem cell transplant; ULN = upper limit of normal

6.15 The baseline characteristics of patients in the studies are shown in Table 5.

Table 5: Baseline characteristics of patients in the studies

	Romidepsin Studies			Pralatrexate Study
	GPI-06-0002 N = 130	**Piekarz, 2011 N = 47**	**Maruyama, 2017 N = 46**	**PROPEL N = 111**
Age, years Median (range) Mean (range)	 61 (20-83) NR	 59 (27-84) NR	 68.7 (8.5) NR	 NR 57.7 (21-85)
Age ≥65 years or ≥60 for Piekarz, 2011, n (%)	49 (38%)	23 (49%)	28 (61%)	40 (36%)
Male, n (%)	88 (68%)	25 (53%)	36 (75%)	76 (68%)
ECOG, n (%) 0 1 2	 46 (35%) 66 (51%) 17 (13%)	 20 (43%) 23 (49%) 4 (8.5%)	 26 (56%) 17 (37%) 7 (15%)	 ≤2 required for enrolment
PTCL Sub-type PTCL NOS AITL ALCL EATL Other	 69 (53%) 27 (21%) 22 (17%) 6 (5%) 7 (5%)	 27 (57%) 7 (15%) 4 (8%) 1 (2%) 8 (17%)	 NR	 59 (53%) 13 (12%) 15 (11.7%) 0 24 (22%)
Prior systemic therapies Median (range)	 2 (1-8)	 3 (1-11)	 NR	 3 (1-12)
Refractory to most recent therapy, n (%)	49 (38%)	NR	NR	69 (63%)
Prior ASCT, n (%)[1]	21 (16%)	18 (38%)	NR	18 (16%)

Source: Table 2-8, pp54-55 of the submission.

AITL. = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ASCT = autologous stem-cell transplant; EATL = enteropathy-associated T-cell lymphoma; ECOG = Eastern co-operative oncology group performance status 0 = no restriction compared to pre-disease, 1 = restricted but able to do light or sedentary work, 2 = ambulatory and able to self-care but unable to work, <50% of waking hours in bed or chair, 3 = some self-care, >50% of waking hours in bed or chair, 4 = unable to self-care, confined to bed or chair, 5 = death; NOS = not otherwise specified; NR = not reported; PTCL = peripheral T-cell lymphoma.

[1] In both GPI-06-002 and PROPEL prior allogeneic stem cell transplant required exclusion.

6.16 Notable features were the high proportion of patients with ALCL, who, current guidelines suggest, should be treated with brentuximab vedotin, the higher proportion of patients with AITL in GPI-06-002, the higher number of prior treatments in PROPEL, and the higher proportion of patients who are refractory to the most recent therapy in PROPEL.

6.17 In the PETAL consortium, data factors most closely associated with worse outcomes in second-line treatment were age >60 years, having been refractory to first-line treatment, having a sub-type other than AITL, having more than one extra-nodal site of disease, having an absolute lymphocyte count below the lower limit of normal, and Ki67 ≥40% (Ki67 is a cellular marker of proliferation; the percentage is the proportion of Ki67 positive tumour cells). Although data are available only for the first three listed factors, two of the three - the higher proportion of patients with AITL and the lower proportion of patients who are refractory to most recent treatment, would favour romidepsin.

Comparative effectiveness

6.18 Results for complete response, partial response and survival in the GPI-06-0002, Piekarz et al., 2011 and PROPEL studies are shown in Table 6.

Table 6: Response and survival in the submitted studies.

	Romidepsin Studies		Pralatrexate Study
	GPI-06-0002 N = 130	Piekarz, 2011 N = 47	PROPEL N = 111
CR + CRu, n (%)	19 (15%)	8 (18%)	12 (11%)
Partial Response, n (%)	14 (11%)	9 (20%)	20 (18%)
Responses (CR + CRu + PR) in patients refractory to most recent treatment, n/N (%)	14/49 (29%)	NR	17/69 (25%)
Duration of Response in Patients with Complete Response, months Median (range)	16.6 (0-34)	29.7 (3-74)	10.1 (3.4-NE)
Progression-free Survival, months Median (95% CI)	4.0 (NR)	NR	3.5 (1.7, 4.8)
CR + CRu + Partial Response by PTCL sub-type, n/N (%)			
PTCL NOS	20/69 (29%)	11/27 (41%)	19/59 (32%)
AITL	8/27 (30%)	1/6 (17%)	1/13 (8%)
ALK-negative ALCL	5/21 (24%)	2/2 (100%)	6/17 (35%)
Other	0/13 (0%)	2/12 (17%)	6/20 (30%)

Source: Constructed during the evaluation from published reports.
AITL = angio-immunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CI = confidence interval; CR = complete response; CRu. = unconfirmed complete response; NR = not reported; PTCL = peripheral T-cell lymphoma.

Comparative harms

6.19 A summary of the common adverse events in the GPI-06-0002, Maruyama et al., 2017 and PROPEL studies are shown in Table 7. Adverse events from Piekarz et al., 2011 were not included as the study reported only treatment related events from each patient's first treatment cycle.

Table 7: Adverse events in the studies

	Romidepsin Studies			Pralatrexate Study	
	GPI-06-0002 N = 130		Maruyama, 2017 N = 46	PROPEL N = 111	
	All events	Grade ≥3	All events	All events	Grade ≥3
Vomiting	51 (39%)	6 (5%)	18 (38%)	28 (25%)	2 (2%)
Diarrhoea	47 (36%)	3 (2%)	16 (34%)	25 (23%)	2 (2%)
Fatigue	72 (55%)	11 (8%)	13 (28%)	40 (36%)	6 (5%)
Thrombocytopenia	53 (41%)	32 (24%)	46 (100%)	45 (41%)	36 (32%)
Neutropenia	39 (30%)	26 (20%)	37 (78%)	26 (25%)	24 (22%)
Anaemia	32 (24%)	14 (11%)	15 (32%)	38 (34%)	20 (18%)
Mucositis	13 (10%)	0	8 (17%)	79 (71%)	24 (22%)

Source: Constructed during the evaluation from published reports.

6.20 Adverse events were similar across the studies, except that mucositis was more common in PROPEL and was a common cause of reduction of pralatrexate dose and an occasional cause of treatment withdrawal.

6.21 Cardiac adverse events were not noted in GPI-06-0002, although tachycardia was noted as a treatment emergent adverse event. However, in the first study of romidepsin in cutaneous T-cell lymphoma, in which the exclusions related to the cardiac effects of romidepsin were not applied, ST or T wave changes in the ECG were reported in 80% of patients and QT prolongation in 9%, and there were two cases of supraventricular arrhythmia and three of ventricular arrhythmia.[14] In Piekarz et al., 2011, one patient with an extensive history of vascular disease died unexpectedly during romidepsin treatment, as a result of which patients with cardiovascular disease were excluded from the study. Cardiac adverse events due to romidepsin may be more frequent in widespread clinical use than in the studies if at-risk patients are less carefully excluded. In Maruyama et al., 2017 there were four cases of atrial fibrillation and two of supraventricular extrasystole reported as adverse events.

6.22 Available data for dose reductions, treatment withdrawal and death are shown in Table 8.

Table 8: Dose reductions, withdrawals and deaths in the studies

	Romidepsin Studies			Pralatrexate Study
	GPI-06-0002 N = 130	Piekarz, 2011 N = 47	Maruyama, 2017 N = 46	PROPEL N = 111
Dose reduction due to AE, n (%)	14 (11%)	20 (42%)	21 (46%)	35 (32%)
Thrombocytopenia	4 (3%)	16 (34%)	NR	2 (2%)
Mucositis	0	0	NR	25 (23%)
Treatment withdrawal due to AE, n (%)	25 (19%)	4 (8%)	13 (28%)	26 (23%)
Thrombocytopenia	3 (2%)	2 (4%)	NR	5 (5%)
Mucositis	0	0	NR	6 (6%)
Death during treatment or within 30 days of last treatment, n (%)	8 (6%)	7 (15%)	2 (4%)	8 (7%)

Source: Constructed during the evaluation from published reports. AE = adverse event; NR = not reported.

Benefits/harms

6.23 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.24 The submission claimed that, compared to pralatrexate, romidepsin is associated with non-inferior effectiveness and different, but non-inferior safety.

6.25 The ESC agreed with the evaluation that the claim with regard to efficacy was not adequately supported by the data presented.

[14] Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2009; 27(32):5410-7.

6.26 The ESC agreed with the evaluation that the claim with regard to safety was not adequately supported by the data presented, but considering the clinical context that it is probably reasonable to conclude that differences in safety between romidepsin and pralatrexate do not provide a reason to prefer one to the other in this patient population as a whole.

6.27 Overall, the ESC considered that the clinical data presented did not allow for a meaningful comparison of romidepsin to pralatrexate to be made. Whilst acknowledging the limitations of the data presented, the ESC was of the view that in the context of a disease where patients have poor survival and limited treatment options, romidepsin would provide clinicians with another valuable treatment option and improve equity of access for patients. The ESC noted that some hospitals are funding romidepsin.

6.28 The PBAC considered that the claim of non-inferior comparative effectiveness was difficult to conclude based on the data available, but on balance, was likely to be reasonable.

6.29 The PBAC agreed with the ESC that the claim of different but non-inferior comparative safety was not adequately supported by the data presented.

Economic analysis

6.30 The submission presented a CMA comparing romidepsin with pralatrexate. The key components and assumptions used in the approach are shown in Table 9.

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Clinical claim: effectiveness	Effectiveness is assumed to be non-inferior to pralatrexate.
Clinical claim: safety	Safety is assumed to be different but non- inferior to pralatrexate.
Evidence base	Informal indirect comparison
Equi-effective doses	Romidepsin 14 mg/m² IV (Days 1, 8, 15; 28-day cycle) is considered equi-effective to pralatrexate 30 mg/m² IV (once weekly for 6 weeks, followed by a 1-week rest; 7-week cycle.
Direct medicine costs	Based on standard dosing for an average patient with a body surface area of 1.8 m^2.
Other costs or cost offsets	Administration Tests for screening or monitoring Concomitant medication Management of key adverse events

Source: Table 3.1, p80 of the submission.

6.31 The equi-effective doses were based on the doses in the Product Information for romidepsin and pralatrexate, and the submission included no allowance for differences in dose intensity.

6.32 The frequency of mucositis in pralatrexate patients used in the analysis was consistent with that observed in the PROPEL study but there was no evidence that all patients with mucositis required hospital admission, and the number of admissions was not included in the data analysis. This cost may therefore be overestimated.

6.33 The submission used the median PFS for both romidepsin and pralatrexate in GPI-06-0002 and PROPEL, as cited in Table 6, Romidepsin PSD, December 2017 PBAC Meeting, as a proxy for duration of treatment. Based on a cycle length of 28 days for romidepsin and 49 days for pralatrexate, the submission determined that the median PFS of 3.5 months equated to 3.8 cycles and 2.17 cycles respectively. Based on the estimated number of cycles, the submission estimated the number of vials per patient to be 34.23 for romidepsin and 39.12 for pralatrexate.

6.34 Differences in body surface area (BSA) would have minimal effect on usage. The mean BSA of Australian cancer patients has been reported to be 1.80 m^2.[15] In a UK study mean values were the same, and the distribution of BSA was close to normal with a standard deviation of 0.18.[16] That is, 95% of patients will have BSA between 1.44 and 2.16 m^2. That range corresponds to a range of romidepsin doses of 20 mg to 30 mg, so, although wastage will vary, the great majority of patients will use three vials per treatment. The dose range for pralatrexate for 95% of patients is 43 mg to 65 mg, so the great majority of patients will use three vials per dose.

6.35 The results of the CMA are shown in Table 10.

[15] Dooley MJ, Singh S, Michael M. Implications of dose rounding of chemotherapy to the nearest vial size. *Supportive Care Cancer* 2004; 12:653-656.

[16] Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: A multicentre retrospective study. *PLoS One* 2010; 5:e8933.

Table 10: Results of the cost-minimisation approach

Proposed equi-effective doses	Pralatrexate 6 doses at 30 mg/m^2 every 49-day cycle for 3.5 months (2.17 cycles)	Romidepsin 3 doses at 14 mg/m^2 every 28-day cycle for 3.5 months (3.80 cycles)
Treatment cost (pralatrexate)		
Dispensed price of pralatrexate per course (13.04 x $3,197.73) [a, b]	$41,713.25	
Administration cost: MBS 13950 (13.04 x $126) [a, c]	$1,643.63	
Concurrent cost of Vitamin B12 ($7.99/3 x 7/10 x (2.17 cycles plus 1) [d]	$6.72	
Concurrent cost of Folic acid ($5.99 / (100/2) x 2.17 cycles) [e]	$12.76	
Calcium folinate cost ($45.60 x 12 x 2.17 cycles) [f]	$1,189.67	
Mucositis admission cost (0.22% x $8,596.50) [g]	$1,891.23	
Total treatment cost per course	$46,457.25	
Cost-minimisation (romidepsin)		
Total treatment cost per course		$46,456.07
Dispensed price of romidepsin per course (11.41 x $3,937.38) [h, i]		$44,951.50
Administration cost: MBS 13950 (11.41 x $126) [c, h]		$1,438.17
Cost of anti-emetic (3 x $3.50 x 3.80 cycles) [j]		$39.95
Baseline ECG cost (100% x $36.45) [k]		$36.45

Source: Calculated from the Attachment 4 economic analysis Excel workbook included in the submission with treatment costs calculated using non-rounded numbers for doses and cycles.

[a] 13.04 doses - derived as follows: 6 x 2.17 cycles. Cycles calculated as follows: 365.25/49 x (3.5/12).

[b] 3 vials of pralatrexate 20 mg per dose based on an average body surface area of 1.8 m^2 (rounded up from 2.7 vials per dose based on efficient funding of chemotherapy principles). Pralatrexate cost based on approved ex-manufacturer price of $1,035.50 x 3 vials plus $91.23 preparation fee.

[c] MBS 13950

[d] Vitamin B12 injection 10 weeks prior to the first dose and every 8-10 weeks thereafter

[e] Folic acid 1 mg per day for 10 days prior and 30 days following pralatrexate

[f] Calcium folinate 90 mg per day x 12 days per cycle administration x 2.17 cycles, based on the recommendation in the EviQ protocol

[g] Admission for Grade 3 or 4 mucositis in 22% of pralatrexate patients; NHCDC Cost Data, Weighted cost of admission for PTCL

[h] 11.41 doses - derived as follows: 3 x 3.8 cycles. Cycles calculated as follows: 365.25/28 x (3.5/12)

[i] 3 vials of romidepsin 10 mg per dose based on an average body surface area of 1.8 m^2 (rounded up from 2.52 vials per dose based on efficient funding of chemotherapy principles). Romidepsin cost based on ex-manufacturer price of $1,282.05 x 3 plus $91.23 preparation fee

[j] 4 x 4 mg ondansetron per dose

[k] MBS Item 11704

6.36 As noted in paragraph 6.32, the analysis includes hospital admission costs for patients with severe mucositis. Removing these costs as well as the over-the-counter cost of the folic acid tablets and recalculating the price per vial would reduce the price by approximately $60 (to $1,226.85). The Pre-PBAC Response argued that patients with R/R PTCL are typically clinically fragile and heavily pre-treated and that it is reasonable to assume that a hospital admission would result from Grade 3 or 4 mucositis.

6.37 The ESC noted that the median PFS for romidepsin, which was used as a proxy for duration of treatment, was 4 months rather than 3.5 months, and that adjusting this parameter would reduce the cost-minimised EMP for romidepsin. The ESC considered it would have been more appropriate to use the reported durations of treatment rather than median PFS and noted that mean duration of treatment was 4.2 months (127.8 days) for romidepsin (based on Coiffier et al., 2012) and mean duration of treatment for pralatrexate was 112.7 days (based on 2.3 cycles of 49 days, as derived

from individual patient data from PROPEL, and as reported in paragraph 5.11 of the Pralatrexate PSD, Dec 2017). The Pre-PBAC Response stated that the median PFS of 4 months that was reported in Coiffer et al., 2012 was rounded up from the median PFS of 3.5 months reported in the previous submissions for romidepsin. The PBAC considered that it would be reasonable to use median PFS of 3.5 months for both romidepsin and pralatrexate as a proxy for duration of treatment.

6.38 The CMA was undertaken using dispensed prices. Pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. Recalculating the submission's CMA at the EMP level would give an EMP for romidepsin of $1,277.74/vial.

Drug cost/patient/course

6.39 Based on the CMA in Table 10 the drug cost per patient per course was estimated as $44,951.50.

Estimated PBS usage & financial implications

6.40 The submission was not considered by DUSC.

The submission presented a market share approach to estimate the likely utilisation and financial impact of listing romidepsin, assuming that romidepsin would substitute for pralatrexate. The key inputs used in the estimates are shown in

6.41 Table 11.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Current pralatrexate PBS market size	Services Australia – PBS Item number reports. for the last complete calendar year and the last 6 years Current PBS Item codes for pralatrexate: 11271F, 11293J, 11278N, 11272G	Reasonable
Current romidepsin utilisation	Sponsor data from patient access program 12 months to June 2025: 295 scripts, 3 vials per script	Unable to be independently verified.
PBS drug prices and co payments	Pralatrexate PBS codes as above plus Ondansetron 5857G, Calcium folinate 5904R	Reasonable
Romidepsin prices and cost	Ex-manufacturer price/10 mg vial: $1,282.05 MA 4 vials DPMA (public hospital) $5,219.43 DPMA (private hospital) $5,336.90 Average cost per script applied in UCM, BSA 1.8m^2 Dose (mg) at 14 mg/m^2* 25.20 Vials 2.52 EFC rounding 3 vials DPMA (public hospital) $3,937.38 DPMA (private hospital) $4,036.90	
Pralatrexate prices and costs	Ex-manufacturer price/20 mg vial: $1,035.50 MA 4 vials DPMA (public hospital) $4,233.23 DPMA (private hospital) $4,336.90 Average cost per script applied in UCM, BSA 1.8m^2 Dose (mg) at 30 mg/ m^2 54.00 Vials 2.70 EFC rounding 3 DP (public hospital) $3,197.73 DP (private hospital) $3,286.90	Reasonable
Market growth	Average 4% per annum derived from PBS service volumes for pralatrexate 2019-2025 Financial year / Total services / Growth 2019/2020 / 908 / - 2020/2021 / 794 / -13% 2021/2022 / 830 / 5% 2022/2023 / 907 / 9% 2023/2024 / 746 / -18% 2024/2025 / 1006 / 35%	The ESC considered that the size of the combined market for romidepsin and pralatrexate would increase with the availability of romidepsin. The ESC considered that romidepsin and pralatrexate could be used sequentially in some patients.
Predicted market share for romidepsin	Sponsor assumption based on international market 20% in year 2026 and 35% in years 2027 - 2031	
Script equivalence	0.88 Calculated as 3 doses per 28 days for romidepsin and 6 doses per 49 days for pralatrexate	Reasonable
MBS prices	Administration:13950 = $126.00 ECG: 11704 = $36.45	Reasonable

Source: Table 4.1, pp89-90 of the submission. DP = dispensed price; DPMA = dispensed price for maximum amount; EFC = efficient funding of chemotherapy; MA=maximum amount

6.42 In its market share approach, as the PBS market for pralatrexate didn't include scripts for patients who received romidepsin on the current compassionate access scheme, the submission increased the market size by carrying forward the number of romidepsin scripts that patients would have been receiving if the compassionate access program were to continue.

6.43 In estimating the market size, the expected utilisation of romidepsin, and the financial impact of listing romidepsin, the submission did not include the cost of potential switch between treatments or combined or sequential treatment and did not consider whether patients receiving romidepsin on the compassionate access scheme may also have been receiving pralatrexate.

6.44 The estimated number of prescriptions and costs as presented in the submission are shown in Table 12.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 49	Year 5	Year 6
Estimated extent of use						
Total scripts	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of romidepsin						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for pralatrexate						
Cost to PBS/RPBS less copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Estimated financial implications for calcium folinate						
Cost to PBS/RPBS less copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Tables 4.6, 4.7, 4.12, 4.13, 4.15. 4.16, pp 93-102 of the submission and Financial Estimates Workbook.
Note: The submission estimated that patient copayments would offset the cost to the PBS/RPBS for ondansetron.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*

6.45 The total cost to the PBS/RPBS of listing romidepsin was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million in the first 6 years of listing.

6.46 The ESC considered that the net cost to the PBS/RPBS of listing romidepsin on the PBS was uncertain and likely underestimated, given:

- romidepsin and pralatrexate may be used in sequence in some patients well enough to receive treatment with a second agent;
- romidepsin and pralatrexate may be used in combination in some patients; and

- the submission's assumption of equal treatment duration and equal dose intensity for romidepsin and pralatrexate may not be realised in clinical practice.

6.47 During the evaluation, the following data (Table 13) was obtained from the DUSC Secretariat for the current use of pralatrexate.

Table 13: DUSC data – pralatrexate patients

Financial year	Incident patients	Prevalent patients
2017/18 (part year)	24	24
2018/19	45	61
2019/20	75	91
2020/21	61	85
2021/22	50	72
2022/23	53	68
2023/24	55	72
2024/25	53	71

Source: Data extracted from the PBS claims database by the DUSC Secretariat, Dec 9, 2025.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 Efficient Funding of Chemotherapy Program listing of romidepsin for the treatment of patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL). The PBAC considered that despite the uncertainties associated with the clinical comparison presented in the submission, it was likely that romidepsin provided similar health outcomes to pralatrexate in the proposed population. The PBAC considered that romidepsin would be acceptably cost-effective if the cost per patient per course was no higher than pralatrexate, assuming the same duration of treatment and relative dose intensity.

7.2 The PBAC noted that PTCL is a heterogenous group of rare cancers, that relapse is common, and that median survival for patients who relapse is low. The PBAC considered there is a high clinical need for additional therapies for R/R PTCL and noted the strong support for romidepsin in the consumer inputs received.

7.3 The PBAC noted that romidepsin is included as a preferred treatment in clinical guidelines and some patients are currently receiving it as part of their treatment regimen (e.g., via hospitals or access program).

7.4 In relation to the proposed listing and restriction the PBAC advised that:

- An Authority Required (Telephone/Online PBS Authorities system) listing was appropriate.
- The proposed maximum amount of 40 mg was appropriate, noting that this would be sufficient for patients with a body surface area of up to 2.8 m^2 (more than 99% of the proposed patient population).

- Clinical criterion stating that 'The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication', should be included. The PBAC noted that this would permit patients to continue to self-fund combination therapy with other non-PBS subsidised agents.
- Flow-on changes to include the above clinical criterion in the current pralatrexate listings 11271F/11293J and 11272G/11278N would be required to preclude the combination use of pralatrexate with romidepsin or other anticancer drugs through the PBS.
- A grandfathering restriction would be required for patients currently being treated with non-PBS subsidised romidepsin.

7.5 The PBAC considered pralatrexate to be the appropriate comparator. The PBAC recalled that it had previously considered pralatrexate to be an appropriate comparator in its consideration of romidepsin in December 2017.

7.6 The PBAC noted that the submission presented an unanchored comparison of romidepsin to pralatrexate based on data from 3 single arm romidepsin studies (GPI-06-0002, Piekarz et al., 2011 and Maruyama et al., 2017) and 1 single arm pralatrexate study (PROPEL) in patients with R/R PTCL. The PBAC considered the data was of low quality for decision making given the unanchored nature of the comparison, and the low patient numbers and the heterogeneity of PTCL in the studies.

7.7 The PBAC considered that the submission's claim of non-inferior effectiveness for romidepsin compared to pralatrexate was difficult to conclude based on the evidence presented. However, the Committee considered that, on balance, noting the response rates presented in Table 6, romidepsin was likely to provide similar health outcomes to pralatrexate.

7.8 The PBAC considered that the submission's claim of different but non-inferior safety for romidepsin compared to pralatrexate was not adequately supported based on the evidence presented. The PBAC noted more thrombocytopenia and cardiac adverse events for romidepsin and more mucositis for pralatrexate. The PBAC considered that romidepsin and pralatrexate have a different safety profile.

7.9 The PBAC noted that the submission had presented a CMA comparing romidepsin to pralatrexate, using median PFS from GPI-06-0002 and PROPEL as a proxy for duration of treatment. Given more accurate data on treatment duration was not available, the PBAC considered use of median PFS was reasonable, noting that this was 3.5 months for both romidepsin and pralatrexate. The PBAC considered that it would be reasonable for the CMA to apply the same relative dose intensity for romidepsin and pralatrexate.

7.10 The PBAC considered the equi-effective doses to be:

- 3 doses of romidepsin at 14 mg/m^2 every 28-day cycle for 3.5 months (3.80 cycles) is equivalent to 6 doses of pralatrexate at 30 mg/m^2 every 49-day cycle for 3.5 months (2.17 cycles).

7.11 The PBAC noted that the CMA included costs for administration, concurrent medication, screening tests and management of adverse events. The PBAC considered the costs for concurrent medication (with the exception of calcium folinate) and screening tests were small and unlikely to be substantially different between romidepsin and pralatrexate. The PBAC advised it was reasonable to exclude these costs from the CMA. With respect to the inclusion of the cost of calcium folinate for pralatrexate, the PBAC noted prophylaxis of mucositis is important and likely to be incurred by all patients, therefore inclusion of the cost of calcium folinate in the CMA was appropriate. The PBAC noted management of severe mucositis was included in the CMA for pralatrexate. The PBAC considered that severe mucositis is rare when treatment protocols that include prophylaxis with calcium folinate are followed appropriately, and as such that the hospital admission costs for mucositis for pralatrexate in the CMA should be removed. The PBAC noted that the CMA should be conducted based on ex-manufacturer prices.

7.12 The PBAC noted that the net cost to the PBS/RPBS over the first 6 years of listing was estimated to be approximately $10 million to < $20 million, given patients currently receiving romidepsin through a patient access scheme would alternatively access romidepsin on the PBS. The PBAC considered the cost of listing romidepsin to be uncertain and likely underestimated. The PBAC considered that there will be some growth in the market because of sequential use of pralatrexate and romidepsin in some patients, however the overall impact would likely be reasonable given the rarity of PTCL.

7.13 The PBAC advised that romidepsin is not suitable for prescribing by nurse practitioners.

7.14 The PBAC advised that, under subsection 101(3BA) of the *National Health Act 1953* romidepsin should not be treated as interchangeable on an individual patient basis with any other drugs.

7.15 The PBAC considered that the Early Supply Rule should not apply.

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because romidepsin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pralatrexate, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT **Form**		**PBS item code**	**Max. Amount**	**№.of Rpts**
ROMIDEPSIN Injection		NEW (Public) NEW (Private)	40 mg	5
Available brands				
Romidepsin (Reach) (romidepsin 10 mg injection [1 vial] (&) inert substance diluent [2 mL vial], 1 pack)				
Restriction Summary [7525] / Treatment of Concept: [7558]				
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
		Prescriber type: ☒Medical Practitioners		
		Restriction type: ☒Authority Required (telephone/online PBS Authorities system)		
Prescribing rule level		**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.		
		Administrative Advice: No increase in the maximum amount or number of units may be authorised		
		Administrative Advice: No increase in the maximum number of repeats may be authorised		
		Indication: Relapsed or chemotherapy refractory Peripheral T-cell lymphoma		
		Treatment Phase: Initial treatment		
		Clinical criteria:		
		The condition must be relapsed or chemotherapy refractory		
		AND		
		Clinical criteria:		
		Patient must have undergone appropriate prior front-line curative intent chemotherapy		
		AND		
		Clinical criteria:		
		The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.		

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
ROMIDEPSIN Injection	NEW (Public) NEW (Private)	40 mg	8
Available brands			
Romidepsin (Reach) (romidepsin 10 mg injection [1 vial] (&) inert substance diluent [2 mL vial], 1 pack)			
Restriction Summary [7545] / Treatment of Concept: [7526]			
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)		
Prescribing rule level	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.		
	Administrative Advice: No increase in the maximum amount or number of units may be authorised		
	Administrative Advice: No increase in the maximum number of repeats may be authorised		
	Indication: Relapsed or chemotherapy refractory Peripheral T-cell lymphoma		
	Treatment Phase: Continuing treatment		
	Clinical criteria:		
	The condition must be relapsed or chemotherapy refractory		
	AND		
	Clinical criteria:		
	Patient must not develop progressive disease while receiving PBS-subsidised treatment with this drug for this condition		
	AND		
	Clinical criteria:		
	Patient must have previously received PBS-subsidised treatment with this drug for this condition		
	AND		
	Clinical criteria:		
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.		
Restriction Summary [New] / Treatment of Concept: [New]			
	Indication: Relapsed or chemotherapy refractory Peripheral T-cell lymphoma		
	Treatment Phase: Transitioning from non-PBS subsidised treatment- Grandfather arrangement		
	Clinical criteria:		
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date]		
	AND		
	Clinical criteria:		
	The condition must be relapsed or chemotherapy refractory		
	AND		
	Clinical criteria:		
	Patient must have undergone appropriate prior front-line curative intent chemotherapy prior to commencing non-PBS subsidised treatment with this drug for this condition		
	AND		
	Clinical criteria:		

	Patient must not have developed progressive disease while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Prescribing Instructions: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

8.2 Flow on Changes to pralatrexate listings for Relapsed or chemotherapy refractory Peripheral T-cell Lymphoma in the initial treatment, (PBS item codes: 11271F/11293J and the continuing treatment (PBS item codes 11272G/11278N) to include:

1- The clinical criterion: '*The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication'* to preclude the combination use of pralatrexate with romidepsin or any other anticancer drug through the PBS for this indication.

Add	**Clinical criteria:**
Add	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.

2- The below AA as administrative change to pralatrexate listings. The current listings for pralatrexate are Authority required listings but lack the administrative advice (AA) that clarifies the authority type.

Add	***Administrative Advice:*** *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.