

7.07 PRALATREXATE, Solution for I.V. infusion, 20 mg in 1 mL, Folotyn®, Mundipharma

1 Purpose of Application

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

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

Component	Description
Population	Adult patients with relapsed or refractory PTCL following first-line chemotherapy.
Intervention	Pralatrexate 30 mg/m ² IV infusion once weekly for six weeks, followed by one week rest, until disease progression or unacceptable toxicity.
Comparator	'Basket of comparator treatments' – DHAP, brentuximab, gemcitabine containing regimens, methotrexate, romidepsin (not PBS listed in Australia), ESHAP, and ICE.
Outcomes	Overall survival, overall response rate, safety.
Clinical claim	Pralatrexate is superior in terms of effectiveness and non-inferior in term of safety compared to the identified 'basket of comparators' in adult patients with relapsed or refractory PTCL.

Source: Table 1.1, p1-8 to 1-9 of the resubmission.

DHAP = dexamethasone, cytarabine, cisplatin, ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; ICE = ifosfamide, carboplatin, etoposide; IV = intravenous; PBS = Pharmaceutical Benefits Scheme; PTCL = peripheral T-cell lymphoma

1.2. The key components presented in the July 2017 resubmission were unchanged from the previous submissions.

2 Requested listing

Suggestions and additions are in *italics* and deletions are in ~~strikethrough~~

Name, Restriction, Manner of administration and form	Max. Amt	Nº. of Rpts	Dispensed price per maximum amount (DPMA)	Proprietary Name and Manufacturer
PRALATREXATE, Solution for I.V. infusion 20 mg in 1 mL	80 mg	5	Effective/Published (public): \$ [REDACTED] / \$ [REDACTED] Effective/Published (private): \$ [REDACTED] / \$ [REDACTED]	Folotyn Mundipharma Pty Ltd.
Category / Program	Section 100, Authority Required (Private and Public Hospital)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Patients who have Relapsed or chemotherapy refractory disease			
Condition:	Peripheral T-cell Lymphoma			

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PBS Indication:	<i>Relapsed or chemotherapy refractory peripheral T-cell Lymphoma</i>
Treatment phase:	<i>Initial treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must demonstrate relapsed or chemotherapy refractory disease to 1st line chemotherapy. AND Patient must have undergone appropriate prior front-line curative intent chemotherapy AND Patient must demonstrate relapsed or chemotherapy refractory disease</p>
Prescriber Instructions	<p>Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed PTCL Pralatrexate PBS Authority Application - Supporting Information Form [to be determined] which includes the following: (i) The date of initial diagnosis of PTCL; (ii) Dates of commencement and completion of front-line curative intent chemotherapy; (iii) a declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory.</p> <p>A maximum quantity and number of repeats to provide for an initial course of pralatrexate of 3 cycles will be authorised as part of the initiating restriction.</p>
Administrative Advice	<p>Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at: www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Note No increase in the maximum number of repeats may be authorised.</p> <p>Note No increase in the maximum quantity or number of units may be authorised.</p> <p>Note Special Pricing Arrangements apply.</p>

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed price per maximum amount (DPMA)	Proprietary Name and Manufacturer
PRALATREXATE, Solution for I.V. infusion 20 mg in 1 mL	80 mg	11	Effective/Published (public): \$ [REDACTED] / \$ [REDACTED] Effective/Published (private): \$ [REDACTED] / \$ [REDACTED]	Folotyn Mundipharma Pty Ltd.
Category / Program	Section 100, Authority Required (Private and Public Hospital)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Patients who have Relapsed or chemotherapy refractory disease			
Condition:	Peripheral T-cell Lymphoma			
PBS Indication:	Relapsed or chemotherapy refractory peripheral T-cell Lymphoma			
Treatment phase:	Continuing treatment			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	Patient must not have progressive disease, And Patient must have previously been issued with an authority prescription for this drug.			
Administrative Advice	Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Note No increase in the maximum number of repeats may be authorised. Note No increase in the maximum quantity or number of units may be authorised. Note Special Pricing Arrangements apply.			

- 2.1. The proposed PBS restriction was similar to that presented in the November 2015 submission. In the March 2016 minor resubmission the Sponsor indicated that they would be willing to restrict the listing of pralatrexate to patients with an Eastern Cooperative Oncology Group (ECOG) performance status of two or less. This restriction criterion was not included in July 2017 proposed listing. The PBAC considered there is no reason to expect prescribers to use this in poor performance status patients given its significant toxicity (mucositis).
- 2.2. The effective dispensed price for the maximum amount was the same as proposed in the March 2016 minor resubmission (which was a [REDACTED] % reduction compared to the original November 2015 submission). As per the previous submissions, the published price was based on an ex-manufacturer price of \$ [REDACTED] per vial.

- 2.3. As per the previous submissions, the July 2017 resubmission presented a cost-utility analysis which was based on a naïve indirect comparison of pralatrexate with a basket of comparator treatments.
- 2.4. The recommended dose of pralatrexate is 30 mg/m² body area, administered by intravenous infusion over 3-5 minutes once per week for six weeks, followed by one week rest (seven week cycle in total). This regimen is to be continued until disease progression or unacceptable toxicity.
- 2.5. The PBAC considered a phone authority would suffice, as there was low risk of use outside the requested use in PTCL.

3 Background

- 3.1. TGA status: Pralatrexate was registered by the TGA in December 2014 for: “The treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy.”
- 3.2. Pralatrexate for the treatment of relapsed or refractory PTCL has been considered by the PBAC on two previous occasions. The first major submission was considered in November 2015 and a minor resubmission was considered in March 2016.
- 3.3. A summary of the outstanding matters of concern to the PBAC are presented in Table 2.

Table 2: Summary of outstanding matters of concern

Matters of concern	How the resubmission addresses it
<p>The submission used a matched controls analysis comparing a subset of patients from the key study, PDX-008, and a historical control cohort.</p> <p>Paragraph 7.3, November 2015 PSD: There was concern about the methodology used in the submission, where the submission presented the most optimistic clinical benefit of a small sub-group of patients in the PDX-008 trial compared to the historical control cohort.</p>	<p>A comparative analysis of all evaluable patients from PDX-008 and the historical control cohort was used to determine OS. There was no patient matching and the majority of available patients were included in the analysis.</p> <p>Although the methods used to determine OS for pralatrexate were more appropriate as they relied on the majority of the patient data, concerns remained about how OS was determined for the historical control cohort, using a stratified Cox regression model.</p>
<p>Paragraph 7.4, November 2015 PSD; paragraph 7.1, March 2016 PSD: There was insufficient evidence of incremental benefits of pralatrexate versus comparators..... The ORR for pralatrexate was not improved compared to brentuximab or combination therapies.</p> <p>Paragraph 7.8, November 2015 PSD; paragraph 7.3, March 2016 PSD: More robust evidence would ideally include other evidence on clinical benefit, such as Quality of Life</p>	<p>Data from an Australian historical control dataset (from the Peter MacCallum Institute) was included in the historical control dataset.</p> <p>Additional supportive pralatrexate and comparator studies were presented in the pooled meta-analysis of ORR. Updated searches were conducted to identify new studies for romidepsin as well. The additional pralatrexate studies consisted of a Japanese study of 25 patients, and two abstracts (one of which was not published). Again, the ORR for pralatrexate was not significantly different from the nominated basket of comparator treatments.</p> <p>No Quality of Life data were presented.</p>
<p>Paragraph 7.5, November 2015 PSD: Study PDX-008 was associated with a high burden of adverse events.</p> <p>Paragraph 7.8, November 2015 PSD; paragraph 7.4, March 2016 PSD: Present more robust evidence to demonstrate the comparative safety of pralatrexate over the comparators.</p>	<p>A pooled analysis and indirect comparison of 13 Grade 3/4 adverse events was presented for pralatrexate and the basket of comparator treatments.</p>

Matters of concern	How the resubmission addresses it
<p>Paragraph 7.6, November 2015 PSD: There was insufficient clinical evidence to support the claim of superior efficacy and non-inferior safety, and therefore the economic evaluation was neither informative nor meaningful. The model was not sufficiently reliable to provide a plausible estimate of value for money. A model should address the concerns raised by ESC including that –</p> <ul style="list-style-type: none"> • Costs were one off up front, rather than accruing over time with treatment; • The proportion of patients in each response state did not vary depending on treatment cycle, resulting in QALYs being driven by survival; • No post-progression treatment costs or consequences, including those related to STC, were included; • Model overall survival estimates in the TreeAge model were inconsistent with the Kaplan-Meier data. <p>Paragraph 7.8, November 2015 PSD: The ICER for brentuximab was in the range of \$45,000 to \$75,000/QALY. An ICER at the lower end of this range would be need in order for pralatrexate to be cost-effective.</p>	<p>The claim of non-inferior safety was supported in the July 2017 resubmission; however, there was insufficient evidence to support the claim of superior efficacy. Thus, the economic evaluation may again not be meaningful.</p> <p>The July 2017 resubmission presented a new economic model which included the following changes:</p> <ul style="list-style-type: none"> • Four treatment states, rather than two; • Costs were accrued with each weekly cycle; • Health states for subsequent treatments were added and post-progression and STC costs were included; • Overall survival estimates were updated and consistent between the TreeAge model and the Kaplan-Meier data; • The number of pralatrexate vials used per patient was based on individual patient data; • PTCL-specific utility values were used. <p>The proportion of patients in each response state did not vary depending on treatment of cycle. This again resulted in QALYs being driven by survival.</p>
<p>Paragraph 7.3, March 2016 PSD: Modifications were made to address costs and allowing for wastage; however, the technical concerns were not.</p>	<p>The ICER presented was at the lower end of the range of \$45,000 – \$75,000 per QALY gained.</p>
<p>Paragraph 7.7, November 2015 PSD: At the price requested the net cost to government may be greater than estimated.</p> <p>Paragraph 7.8, November 2015 PSD; paragraph 7.4, March 2016 PSD: Revised financial estimates were required.</p>	<p>Updated financial estimated were provided which included:</p> <ul style="list-style-type: none"> • 40 vials of pralatrexate used per patient on average; • increased uptake assumptions; • corrected costs for folic acid and Vitamin B₁₂; • substantial alterations to costs for comparator treatment; and • costs associated with stem cell transplant.

Source: compiled during analysis

ESC = Economic Sub-Committee; ICER = incremental cost-effectiveness ratio; ORR = overall response rate; OS = overall survival; PTCL = peripheral T-cell lymphoma; QALY = quality-adjusted life year; STC = stem cell transplant

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

4 Population and disease

- 4.1. PTCL is a rare form of non-Hodgkin lymphoma that has a poor prognosis, with a five year overall survival (OS) estimated between 20% and 37%. The median OS in patients who relapse or are refractory to first-line treatment was reported to be approximately 6.5 to 8.0 months.
- 4.2. Pralatrexate was proposed as a second-line agent for the treatment of relapsed or refractory PTCL. The PBAC had previously considered that a second- or later-line listing was the appropriate clinical place for pralatrexate (paragraph 7.8, November 2015 PSD). The ESC confirmed that the clinical place in therapy for pralatrexate was second-line or later.

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

5 Comparator

- 5.1. The nominated comparator was: a basket of comparator treatments that included dexamethasone, cytarabine and cisplatin (DHAP); brentuximab; gemcitabine containing regimens; methotrexate; romidepsin; etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP); and ifosfamide, carboplatin and etoposide (ICE).
- 5.2. The PBAC had previously accepted that the basket of comparator treatments was the appropriate main comparator (paragraph 7.2, November 2015 PSD). While the PBAC had accepted that a basket of comparators was appropriate, it does not accept the inclusion of brentuximab in the costings for the basket when the drug is neither included in the clinical comparison basket nor will be replaced by pralatrexate if listed.
- 5.3. As per the previous submissions, the basket of comparator treatments was used in the determination of overall response rate (a secondary outcome), and incorporated into the economic model and financial estimates. In this submission it was also used to determine safety.
- 5.4. In the previous submissions, although romidepsin was nominated in the basket of comparator treatments, it was not included in the evaluation of efficacy (overall response rate). In this resubmission romidepsin was considered to be a near market comparator and it was included in the evaluation of efficacy (overall response rate) and safety. This was appropriate, since a major submission seeking PBS listing for romidepsin for the treatment of PTCL was considered (and rejected) by the PBAC in November 2016. The ESC considered that while there was no clear evidence on whether pralatrexate would be used prior to or post romidepsin, it was a reasonable near market comparator. The PBAC considered that romidepsin was a reasonable near market comparator.
- 5.5. For the determination of the primary outcome, OS, the basket of comparators was again not used. Instead the submissions utilised a historical control cohort – see Section 6 below for how this differed from the previous submissions.
- 5.6. The PBAC noted neither the international historical control series (1/386) nor the Australian control series (0/34, and 0/83 total) included brentuximab as a significant contributor to the basket of therapies, yet it is included in the basket of therapies used in the economic evaluation, and has a high weighting (>20%). No evidence of OS advantage has been provided in comparison with brentuximab. In Australian practice it is highly improbable that current brentuximab use in the subset of PTCL patients with CD30+ anaplastic large cell lymphoma will be replaced by pralatrexate should it be PBS listed.

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

6 Consideration of Evidence

Sponsor hearing

- 6.1. The sponsor requested a hearing for this item. At the hearing, a clinician discussed the case studies to highlight the benefit of pralatrexate treatment in an area of high clinical need. The clinician indicated that of the several subtypes of PTCL, brentuximab vedotin and romidepsin were the preferred treatment options for small anaplastic large cell lymphoma (sALCL) and angioimmunoblastic T-Cell Lymphoma (AITL), respectively. The clinician also stated that nausea, fatigue and grade 3 mucositis were the most commonly observed AEs resulting from pralatrexate treatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on treatment selection for patients with PTCL, including how choices can differ for the various histologies that constitute PTCL.

Consumer comments

- 6.2. The PBAC noted and welcomed the input from health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments highlighted the tolerability and effectiveness of pralatrexate in patients with PTCL. The PBAC also noted Rare Cancer Australia's support for PBS listing of pralatrexate, claiming its effectiveness in extending survival, and the potential benefits of its use in advance of, or in combination with, romidepsin. The PBAC noted that this advice was not supported by the evidence provided in the submission.

Clinical trials

- 6.3. For the determination of OS the resubmission was based on a naïve indirect comparison of:
- Pralatrexate: study PDX-008 (N = 115); single-arm, open label and
 - Combined historical control cohort which consisted of patients from:
 - Four international lymphoma databases: Memorial Sloan-Kettering Cancer Centre, University of Nebraska Medical Centre, Groupe d'Etude des Lymphomes de l'Adulte and the Samsung Medical Centre (N = [REDACTED]). These data were included in the previous submissions; and
 - One Australian database: Peter MacCallum Institute (N = [REDACTED]). These data were new to this resubmission.
- 6.4. The previous submissions utilised PDX-008 and the international database to obtain a matched patient cohort (n = 66 in each arm) for the comparison of OS. The PBAC were concerned about the methodology used in the submission and that the submission presented the most optimistic clinical benefit for a small sub-group of patients in the PDX-008 trial compared to the historical control cohort (paragraph 7.3, November 2015PSD). It was likely that the matched population represented a

healthier population than the overall efficacy evaluable population, biasing the hazard ratio in favour of pralatrexate (paragraph 6.11, November 2015 PSD).

- 6.5. Therefore, this resubmission used a comparative analysis set to analyse OS. This utilised all eligible patients from study PDX-008 (n = [REDACTED]/115), the four international databases (n = [REDACTED]) and the additional Australian database (n = 34/83). The eligibility criteria (see Table 5) were applied to patients to ensure that the characteristics of the patients were comparable and consistent with the proposed PBS restriction.
- 6.6. Details of study PDX-008 and the historical control cohorts presented in the resubmission are provided in the table below.

Table 3: Key studies and associated reports presented in the July 2017 resubmission

Study ID	Protocol title/Publication title	Publication citation
Pralatrexate: non-randomised studies		
PDX-008	Allos Therapeutics PDX-008: A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma.	29 April 2010 CSR
	O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Lechowicz MJ, Savage KJ, Shustov AR, Gisselbrecht C, Jacobsen E, Zinzani PL, Furman R, Goy A, Haioun C, Crump M, Zain JM, His E, Boyd A, Horwitz S. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study.	2011 J Clin Oncol. 29(9): 1182-1189
	O'Connor O, Zinzani PL, Koutsoukos T, Coiffier B. Pralatrexate reverses the trend in progressive resistance with successive chemotherapy regimens in the treatment of relapsed or refractory peripheral t-cell lymphoma (PTCL).	2011 Haematologica. 96: 151-152
	Foss FM, Horwitz SM, Pinter-Brown L, Goy A, Pro B, Coiffier B, Popplewell L, Savage KJ, Shustov A, Zain JM, Koutsoukos T, Fruchtmann SM, O'Connor OA. Pralatrexate is an effective treatment for heavily pre-treated patients with relapsed/refractory transformed mycosis fungoides (TMF).	2010 Blood. 116 (21)
	Foss F, Horwitz SM, Coiffier B, Bartlett N, Popplewell L, Pro B, Pinter-Brown LC, Shustov A, Furman RR, Haioun C, Koutsoukos T, O'Connor OA. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study.	2012 Clin Lymphoma Myeloma Leuk. 12(4): 238-243
	Goy A, Pro B, Savage KJ, Bartlett NL, Lechowicz MJ, Jacobsen ED, Young F, Crump M, Borghaei H, Link B, Fruchtmann SM, O'Connor OA. Pralatrexate is effective in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with prior ifosfamide, carboplatin, and etoposide (ICE)-based regimens.	2010 Blood. 116 (21)
Comparator treatments		
Historical control	Individual patient data 4 overseas databases (combined) 1980-2011	August 2013 Allos Therapeutics Ltd. Historical Controls Data Report.
Historical control	Individual patient data – patients with relapsed or refractory PTCL Australia 1989-2015	2015 Peter MacCallum Cancer Institute

Source: Table 2.4, pp 2-19 to 2-20; Table 2.15, p 2-48 of the resubmission

CSR = clinical study report; Nov 15; ICE = ifosfamide, carboplatin, and etoposide; PTCL = peripheral T-cell lymphoma; TMF = transformed mycosis fungoides

6.7. The key features of study PDX-008 and the historical control cohorts are summarised in the table below.

Table 4: Key features of the included evidence – naïve indirect comparison

Trial	N	Design/ Duration of follow-up	Risk of bias	Patient population	Outcomes	Used in economic model?
Pralatrexate						
PDX-008	115 ([REDACTED] ^a)	OL, MC 2 years	High	Progressed after ≥ 1 prior treatment	ORR, OS, PFS, safety	Yes
Historical control cohort						
International databases	[REDACTED] ([REDACTED] ^a)	Historical database 1980-2011	High	Received ≥ 1 prior therapies	OS	Yes
Australian database	[REDACTED] ([REDACTED] ^a)	Historical database 1989-2015	High	All PTCL patients	OS	Yes

Source: compiled during the evaluation

MC = multi-centre; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PTCL = peripheral T-cell lymphoma

^a Number of patients included in comparative analysis set

6.8. The criteria outlined in the table below were applied to study PDX-008 and the international and Australian databases to identify patients for inclusion in the comparative analysis set. The criteria were applied to ensure that the characteristics of patients from the different data sources were comparable and consistent with the proposed PBS restriction. The criteria were appropriate.

Table 5: Patient eligibility criteria for the comparative analysis

Eligibility criteria	Rationale
≥ 1 prior line of therapy	To ensure the population only included relapsed/refractory PTCL patients, and to provide consistency with the PDX-008 and the proposed PBS population.
Provision of survival times that allowed calculation of OS	Primary analysis outcome and thus mandatory to have sufficient data to allow OS to be calculated.
ECOG ≤ 2	PDX-008 restricted inclusion to ECOG ≤ 2. Performance status is significantly associated with OS, therefore it was important that patients in the comparison had similar ECOG scores.
Not received SCT (autologous or allogeneic) as last line of therapy	The comparator is a 'basket of treatments', i.e. not SCT, and additionally SCT is assumed to be associated with improved OS (Lunning 2013). Patients could have SCT as a prior line of therapy, but not as their last line of therapy.
Not received an investigational therapy	To allow a comparison with the PBS-listed basket of comparator treatments.
Histologically confirmed PTCL, not primary CNS lymphoma.	Primary CNS lymphoma is treated with different chemotherapy regimens, not pralatrexate nor comparators.

Source: Table 2.22, pp2-61 of the resubmission

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; PTCL = peripheral T-cell lymphoma; SCT = stem cell transplant

- 6.9. The eligibility criteria for the comparative analysis set required an ECOG score of two or below. This was comparable with the inclusion criteria of study PDX-008. This addressed a concern with the November 2015 submission that patients from PDX-008 were not matched to historical controls on the basis of ECOG status and may have resulted in PDX-008 patients in the matched cohort having a better performance status than those from the historical control (paragraph 6.11, November 2015 PSD).
- 6.10. The criteria were consistent with the proposed PBS restriction in terms of number of prior lines of therapy and histologically confirmed PTCL, noting that although patients in the PDX-008 trial had a median of 3 lines prior therapy, the PBAC had considered that a second or later line listing was the appropriate clinical place for pralatrexate (paragraph 7.8, November 2015 PSD).
- 6.11. The ESC considered that the removal of patients treated with experimental therapies from the OS analysis potentially enriched the remaining population for patients with less aggressive disease, and therefore those who would potentially have a better outcome.

Comparative effectiveness

Overall survival

- 6.12. Pralatrexate results were based on a follow-up period of two years. Median OS using the evaluable population (n = 109) was 14.5 months (95% confidence interval (CI): 10.6, 22.5).
- 6.13. To compare OS between PDX-008 and the combined historical control, a stratified Cox regression model was created to provide predictions for survival. The multivariate analysis incorporated [REDACTED].
- 6.14. The ESC noted that prognostic factors such as [REDACTED] not matched for, and therefore considered that this could affect the independence of the true 'drug effect', as calculated in the multivariate analysis.
- 6.15. The use of the stratified Cox model might not have been appropriate to estimate median OS for the combined historical control cohort.
- The PSCR (p.2) acknowledged that there were other methods to provide an estimate, such as a weighted Kaplan-Meier analysis; however, the Cox regression model used was the most robust. The PSCR (p.2) also acknowledged that there were a number of limitations to using a stratified approach to allow for non-proportionality, while reiterating that the approach used was the best choice for the application.
 - The PSCR (p.3) disagreed with the view that the effect of the Cox regression model on the OS estimate for the historical control cohort was unknown and might have over or underestimated survival. The PSCR argued that the goodness

of fit exercise that was conducted, overlaying the Cox model estimate onto the Kaplan-Meier curve for the individual pralatrexate patient data showed the modelling approach was appropriate. The ESC considered that while this was likely to be a reasonable argument for the pralatrexate estimates, the Committee remained uncertain as to whether the same goodness of fit applied for the historical control cohort, as no individual patient data were available for comparison with the modelled estimates. The PBAC noted the Pre-PBAC response to this issue.

- Further, the ESC considered that although of potential clinical relevance, the Australian cohort was very small (█ events from █ eligible patients), and therefore considered that any analysis conducted comparing this cohort to the OS cohort, would be statistically underpowered. The small size of the Australian cohort also meant that a robust determination of differences in the distribution of key confounders between the local and OS historical cohorts was difficult, as the difference between a genuine non-difference and an underpowered (and thus undetectable) difference, would be difficult to estimate.

6.16. Table 6 and Figure 2 present the estimated median OS across a series of Kaplan Meier analyses stratified by each cohort and for the combined historical control cohort. The hazard ratio is presented for the combined historical control cohort.

6.17. The resubmission proposed a minimal clinically important difference (MCID) of three to five months improvement in median OS, and a █% to █% improvement in the hazard ratio (i.e. a hazard ratio less than █ to █). The MCID was derived from deliberations of an expert consensus panel of the American Society of Clinical Oncology working groups (Ellis 2014). The ESC considered that the nominated MCID (median █ months' improvement in median OS; HR █) was likely to be reasonable. The PBAC agreed that for assessment of well conducted randomised trials such values would represent a reasonable MCID.

Table 6: Predicted median overall survivals – comparative analysis set

	Pralatrexate		Historical control cohort	
	PDX-008	International databases	Australian database	
N	█	█	█	
Events, n	█	█	█	
Median OS, months (95% CI)	██████████	██████████	██████████	
		Combined: ██████████		
HR (95% CI) ^{a, b}	██████████			
November 2015/March 2016 submissions				
N	66	66	NA	
Median OS, months (95% CI)	19.0 (11.4, NE)	5.8 (3.5, 8.0)	NA	
HR (95% CI)	0.394 (0.26, 0.60)			

Source: Table 2.43, p2-101; Table 2.44, p2-104 of the resubmission

CI = confidence interval; HR = hazard ratio; NA = not applicable; NE = not estimable; OS = overall survival

^a HR for PDX-008 versus international databases = ██████████

^b HR for PDX-008 versus Australian database = ██████████

Figure 1: KM curves for OS for PDX-008 versus the combined historical control cohort (control)



- 6.18. Data from the comparative analysis set resulted in a median OS of 14.7 months (95% confidence interval (CI): [REDACTED]) for pralatrexate patients and [REDACTED] (95% CI: [REDACTED]) for the combined historical cohort (Figure 1). The absolute difference in median OS was [REDACTED], which was greater than the identified MCID of three to five months. The combined hazard ratio of OS was [REDACTED] (95% CI: [REDACTED]) (the point estimate and the upper 95% CI exceeded the nominated MCID of [REDACTED]).
- 6.19. The OS estimate for patients from the Australian database was [REDACTED] (95% CI: [REDACTED]). This was not statistically significantly different from that estimated for patients in PDX-008 (14.7 months, 95% CI: [REDACTED]). The absolute difference in median OS ([REDACTED]) and the reduction in the rate of death (HR: [REDACTED], 95% CI: [REDACTED]), did not meet the nominated MCIDs. The ESC noted the PSCR (p.1) disagreed, and presented a different analysis showing a statistically significant difference in OS when comparing pralatrexate to the Australian patient dataset. The ESC reaffirmed that the size of the Australian cohort meant that any comparisons conducted were statistically underpowered, and therefore unreliable.
- 6.20. The ESC considered that the chief limitation of the patient cohorts (PDX-008; Overseas Control; and Local Control) was the non-random assignment, given that the key confounders may be imbalanced across the 3 patient cohorts. As such, it was difficult to determine whether the estimated difference in OS was attributable to the treatment, or to systematic differences between patient cohorts in terms of

prognostic correlates (as noted above in paragraph 6.12, not all relevant prognostic factors were match for). The ESC considered that it was unclear whether any of the multivariate Cox models presented in the resubmission were tested for interactions between pairs of highly correlate model covariates. Further, it was unclear whether stem cell transplant status was associated with OS from the statistical models presented in the resubmission.

6.21. The PBAC considered the confounding cannot be overcome fully, neither by approaches taken in the current application, nor the matched analysis used previously.

Overall response rate

6.22. The July 2017 resubmission presented an updated supportive pooled meta-analysis and naïve indirect comparison of overall response rates. Three newly identified pralatrexate studies and six newly identified studies relating to the basket of comparative treatments, including five new romidepsin studies, were included in the analysis.

Table 7: Overall response rates for pralatrexate and the basket of comparator treatments

	N	n, events	Response assessor	ORR (95% CI)
Pralatrexate				
PDX-008	■	■	Independent review	■
		■	Investigator	■
PDX-JP1 (Japanese study)	■	■	Independent review	■
FOT12-CN-301 (abstract only, not published)	■	■	Investigator	■
O'Connor 2015 (abstract only)	■	■	Investigator	■
Pooled	■	■	Independent review	■
		■	Investigator	■
Brentuximab				
Pooled	■	■	Independent review	■
		■	Investigator	■
Gemcitabine-containing regimens				
DHAP	■	■	Investigator	■
ESHAP	■	■	Investigator	■
ICE	■	■	Investigator	■
Romidepsin				
Pooled	■	■	■	■
Mixed comparator treatments				
Pooled	■	■	■	■

Source: Table 2-64, p2-131; Figure 2-16, p2-132 of the resubmission; and Table 14.2.3, pp155-163 of the PDX-008 CSR
 CI = confidence interval; DHAP = dexamethasone, cytarabine, cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin;
 ICE = ifosfamide, carboplatin, etoposide; NR= not reported; ORR = overall response rate

- 6.23. The updated pooled overall response rates were similar to those presented in the November 2015 submission. Again, the rates for pralatrexate (both investigator and independent review) were not significantly different from any of the pooled rates for the nominated basket of comparator treatments.
- 6.24. The PSCR (p.3) states the relationship between ORR and OS in R/R PTCL is not direct, linear nor predictable, as it is markedly influenced by the duration of therapy that can be tolerated by patients. The PBAC agreed with ESC that while the absence of a response advantage for pralatrexate did not preclude delivery of a survival advantage, its absence reduced confidence in the magnitude of the survival benefit claimed in this non-randomised comparison.

Comparative harms

- 6.25. From study PDX-008, it was reported that 25% of pralatrexate patients experienced at least one treatment-related serious adverse event, 26% experienced a treatment-related Grade 4/5 adverse event and 38% of patients experienced a Grade 3 treatment-related adverse event.
- 6.26. In study PDX-008 the most commonly reported adverse events (AEs) (Grade 1 to 4) associated with pralatrexate were mucosal inflammation (68%), thrombocytopenia (40%), nausea (33%), anaemia (32%), fatigue (30%), neutropenia (24%) and epistaxis (23%). The PSCR (p.4) stated that while the most common Grade 3 or 4 AE seen with pralatrexate is mucositis (22%), it was clinically manageable with dose reduction or discontinuation. The pre-PBAC response (p.1) argued that the toxicity observed in PDX-008 study was predictable, and the most commonly observed AEs, mucositis and thrombocytopenia, were usually manageable, allowing ongoing therapy with discontinuation rates of 6% and 5% of cases, respectively. The PBAC considered Grade 3/4 mucositis to be a significant morbidity, regardless of whether it was predictable, and noted the 23% discontinuation rate due to AEs in the trial.
- 6.27. The previous submissions did not present comparative safety data. This resubmission presented a pooled analysis and naïve indirect comparison of Grade 3 or 4 AEs between pralatrexate and the basket of comparator treatments – see Table 8.

Table 8: Pooled estimated rates of Grade 3 or 4 adverse events with pralatrexate and the basket of comparator treatments (occurring in ≥ 10% of patients)

	Pralatrexate	Brentuximab	DHAP	ESHAP	Gemcitabine-containing	ICE	Romidepsin
Number of studies	3	2	4	4	10	1	1
Max. patients ^a	193	93	487	150	543	40	131
Adverse event	Estimated rate, % (95% CI)						
Peripheral neuropathy	0.9% (0.1, 6.3)	10.9% (5.9, 19.1)	4.4% (1.2, 11.0)	4.0% (0.1, 20.4)	4.4% (2.0, 9.4)	10.0% (2.8, 23.7)	-
Neutropenia	21.3% (16.1, 27.6)	18.5% (11.8, 27.8)	73.8% (41.2, 91.9)	82.1% (19.6, 98.9)	44.3% (29.3, 60.5)	90.0% (76.3, 97.2)	18.3% (12.1, 26.0)
Thrombocytopenia	31.7% (25.5, 38.6)	11.5% (6.3, 20.1)	56.2% (31.1, 78.5)	72.3% (4.6, 99.3)	37.3% (25.1, 51.3)	90.0% (76.3, 97.2)	22.9% (16.0, 31.1)
Anaemia	16.6% (12.0, 22.6)	6.5% (2.9, 13.7)	30.8% (17.0, 47.6)	-	21.5% (15.3, 29.5)	-	5.3% (2.2, 10.7)
Nausea	3.4% (1.3, 8.2)	1.7% (0.0, 9.2)	8.5% (6.0, 11.9)	21.9% (9.3, 40.0)	5.3% (3.5, 7.8)	5.0% (0.6, 16.9)	1.5% (0.2, 5.4)
Vomiting	1.8% (0.2, 6.4)	3.4% (0.4, 11.9)	6.9% (4.3, 10.4)	21.9% (9.3, 40.0)	7.2% (5.2, 9.9)	-	3.8% (1.3, 8.7)
Infection	1.2% (0.2, 5.5)	5.7% (2.1, 14.3)	21.3% (14.6, 30.1)	37.5% (21.1, 56.3)	12.3% (9.6, 15.8)	12.5% (4.2, 26.8)	6.1% (2.7, 11.7)
Febrile neutropenia	4.7% (2.1, 10.0)	1.7% (0.0, 9.2)	25.1% (21.2, 29.4)	44.6% (29.5, 60.7)	13.1% (8.8, 19.0)	12.5% (4.2, 26.8)	3.8% (1.3, 8.7)
Stomatitis/mucositis	20.7% (15.6, 27.0)	-	-	40.6% (23.7, 59.4)	5.8% (2.6, 12.4)	-	0% (0.0, 2.8)

Source: Table 2-65, pp2-130 to 2-131 of the resubmission

CI = confidence interval; DHAP = dexamethasone, cytarabine, cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; ICE = ifosfamide, carboplatin, etoposide

^a Maximum N value for any listed adverse event. For some adverse events fewer patients contributed data.

Benefits and harms

6.28. The naïve indirect comparison presented in the resubmission did not allow for a comparison of the benefits and harms of pralatrexate and the basket of comparator treatments beyond what has been presented above. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.29. The clinical claim presented in this resubmission was that pralatrexate was superior in effectiveness and had comparable or non-inferior safety compared to the basket of comparator treatments. This was unchanged from the November 2015 submission. The March 2016 minor resubmission did not explicitly state a clinical claim.

6.30. Previously, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data (paragraph 6.21, November 2015 PSD).

6.31. In the July 2017 resubmission the claim of superior effectiveness was not adequately supported by the evidence as:

- It was based on naïve indirect comparisons of patients from numerous different sources with considerable heterogeneity;
- The use of the stratified Cox regression model to estimate median OS might not have been appropriate and the effect on the combined historical control cohort (i.e. whether it over or underestimated survival) was unknown. The ESC noted the goodness of fit exercise that was conducted, overlaying the Cox regression model estimate onto the Kaplan-Meier curve for the individual pralatrexate patient data could not be applied for the historical control cohort, as no individual patient data were available for comparison with the modelled estimates. The PBAC considered this to be a major limitation.
- The estimated median OS of pralatrexate patients (14.7 months; 95% CI: [REDACTED]) was not significantly different from the median OS estimate for patients from the Australian database, [REDACTED] (95% CI: [REDACTED]). In addition, the absolute difference of [REDACTED] and the hazard ratio of death of [REDACTED] (95% CI: [REDACTED]) did not reach the identified MCIDs. The ESC considered that although of potential clinical relevance, the Australian cohort was small, and therefore any comparison to it would be statistically underpowered, and therefore unreliable. The ESC considered that the small size of the Australian cohort also meant that differences in the distribution of key confounders between the local and OS historical cohorts were difficult to determine.
- The treatments received by patients in the combined historical control cohort were not representative of the nominated basket of comparator treatments. Approximately 66% of patients from the international database had not received a therapy from the basket of comparator treatments as their most recent therapy and patients in the Australian dataset were excluded if they had been previously treated with romidepsin. The ESC considered that the removal of patients treated with experimental therapies from the OS analysis, potentially enriched the remaining population for patients with less aggressive disease, and therefore those who would potentially have a better outcome.
- The updated pooled overall response rate for pralatrexate (both investigator and independent review) was not significantly different to any of the pooled rates for the nominated basket of comparator treatments. This did not support the large gain in OS presented. The ESC noted better OS results are largely due to the better tolerability and longer duration of response rather than ORR, i.e. patients remain on better tolerated longer resulting in better OS.
- The ESC noted that the PBAC had previously requested further evidence on clinical benefit, such as Quality of Life (QoL) data (pralatrexate PSDs, November 2015 and March 2016 PBAC meetings). However, the PSCR (p.3) stated that no QoL data directly related to pralatrexate were available, as QoL was not

measured in the key PDX-008 trial. The PSCR further stated that due to the limited survival seen and lack of comparative studies in R/R PTCL, QoL measurement is not usual in this therapy area. The ESC considered that even a qualitative description of QoL improvements in patients who respond to treatment would be useful in determining the magnitude of benefit, if any, derived from pralatrexate compared to the basket of comparators. The pre-PBAC response (p.2) claimed that pralatrexate did not demonstrate any significant cumulative toxicity, nor any adverse impact on QoL, making it suitable for longer term therapy, and argued that extremely poor tolerability is often reported for multi-agent combination therapies included in the 'basket of comparators'.

- 6.32. The PBAC considered that pralatrexate was active against previously treated PTCL, and that it was likely to have greater efficacy than historical chemotherapy combinations. However, the increment in efficacy remains uncertain. Further, the relative efficacy of pralatrexate and romidepsin, the near market comparator, has not been determined. 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 than observed for pralatrexate (8.0 vs 3.4 mths, respectively; O'Connor ASH 2015).
- 6.33. Previously, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data (paragraph 6.22, November 2015 PSD). In this resubmission, the claim of non-inferior safety was supported by comparative evidence. The PBAC agreed that safety was non-inferior to other chemotherapy regimens, but that the rates of severe mucositis and discontinuations due to AEs were substantial and indicated that the treatment had significant toxicity.

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

Economic analysis

- 6.34. The ESC noted structural improvements had been made to the economic model, but this did not resolve the underlying issues regarding clinical effectiveness. A simplified extrapolation of the claimed OS gain may have better informed PBAC of the economic consequences of accepting pralatrexate for PBS listing in PTCL.
- 6.35. In November 2015 the PBAC considered that the economic evaluation was neither informative nor meaningful given the clinical evidence did not support the clinical claim (paragraph 7.6, November 2015 PSD). Although the July 2017 resubmission provided evidence to support the claim of non-inferior safety, the evidence to support the claim of superior efficacy remained insufficient.
- 6.36. In November 2015 the PBAC noted that the economic model was not sufficiently reliable to provide a plausible estimate of value for money for the listing of pralatrexate (paragraph 7.6, November 2015 PSD). The July 2017 model addressed most of the issues raised by the PBAC and ESC (see below) and was considered more reliable; however some structural and input issues remained (see below).

- 6.37. The resubmission presented a stepped cost-utility analysis. The new model included the following key changes to that presented in the November 2015 submission:
- There were four treatment states (primary treatment, treatment pause, subsequent treatment and dead) rather than two (alive and dead). The ESC considered that a four-health state model may have been reasonable, but noted that despite approximately a quarter of patients in the PDX-008 study discontinuing pralatrexate due to AEs, the model did not have a discontinuation state. Acknowledging that discontinuations may have been captured elsewhere in the model, the ESC considered that the inclusion of a discontinued health state would have increased its transparency;
 - Costs were accrued with each weekly cycle, rather than one off, up-front costs;
 - The model allowed for the inclusion of post-progression subsequent therapy costs;
 - Cost associated with stem cell transplants were incorporated;
 - OS estimates in the TreeAge model were consistent with the Kaplan-Meier data;
 - Individual patient data were used to calculate the average number of pralatrexate vials used; and
 - PTCL-specific utility values were used.
- 6.38. A number of structural issues were identified with the new model including:
- OS for pralatrexate patients was overestimated (■■■ months) in the economic model, when compared to results from PDX-008 (■■■ months). As such, the ESC considered that the unreliable survival input was further confounded, resulting in greater degree of uncertainty in the economic model. The pre-PBAC response (p.3) argued that the economic model did not overestimate the OS of PDX-008 patients at ■■■ months because this was the Cox-regression adjusted OS of patients;
 - All patients were eligible to receive a stem cell transplant after 27 weeks, regardless of treatment success. The ESC noted this was not a realistic assumption and successful treatment with pralatrexate (if superior to other therapies) may actually lead to more SCT than for the comparator; and
 - The application of adverse event probabilities, costs and disutilities after four weeks, rather than at the commencement of treatment. The PSCR (p.5) claimed that applying the adverse event costing and disutilities at 4 weeks into the model cycle was reasonable, given that it takes time for treatment toxicities to accumulate.
- 6.39. As per the economic model presented in the November 2015 submission, there was no variation in the proportion of patients entering each health state following treatment with pralatrexate or the comparator. This meant that the resultant gain in quality-adjusted life years (QALY) was again driven by survival differences, rather

than any changes in response to treatment. To address this issue, the PSCR (p.4) presented a new analysis to determine the treatment responses of the historical comparison cohort. The analysis was conducted on █ of the potential █ available patients (█ international and █ Australian). The ESC noted that utilising the updated response rates for the comparator arm presented in the PSCR (p.4) resulted in an incremental QALY gain of █ compared to █ in the resubmission base case, and a resultant ICER at the lower end of the range of \$45,000-\$75,000/ QALY increased from \$45,000-\$75,000/ QALY.

- 6.40. The PBAC noted the ESC’s advice, as well as the analyses provided in the submission and the arguments from the pre-PBAC response. The PBAC considered that the deficiencies in the primary clinical data required the model to include many important assumptions, and collectively these problems mean that the output of the model is both uncertain and probably optimistic.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 2 years in study PDX-008. The OS curves converged at 5 years, with no additional incremental costs or benefits; thus, the model base case was essentially 5 years.
Outcomes	LYG and QALYs
Methods used to generate results	A discrete-time Markov model with microsimulations
Health states	The model consisted of 4 treatment states: primary treatment, treatment pause, subsequent treatment or death, from which (except from death) patients could enter one of 4 health states: CR (+ CRu), PR, SD, PD (+ UR) (November 2015 model structure had 2 treatment states – alive and dead.)
Utilities	Trial based; PTCL specific from Kang 2015 (abstract only) (November 2015 submission used utility values for relapsing and/or refractory Hodgkin lymphoma and sALCL from Swinburn 2012 – these utilities were used in a sensitivity analysis)
Cycle length	1 week (November 2015 submission used 1 month)
Transition probabilities	For primary treatment: Sourced from Study PDX-008 and used in both the pralatrexate and control arms. For subsequent treatment: Sourced from Australian historical dataset and used in both the pralatrexate and control arms.

Source: Table 3.1, p3-5 of the resubmission

CR = complete response; CRu = complete response unconfirmed; LYG = life years gained; PD = progressive disease; PR = partial response; PTCL = peripheral T-cell lymphoma; QALY = quality-adjusted life year; sALCL = systemic anaplastic large-cell lymphoma; SD = stable disease; UR = unevaluable response

- 6.41. The key drivers of the model are summarised in the table below. The drivers differ from those presented previously as the model was significantly different.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Extrapolation of overall survival in the pralatrexate arm overestimated survival, when compared to rates from PDX-008.	High, favours pralatrexate
Cost of basket of comparator treatments	Weighted based on results of the Expert clinician survey (N = ■■■); costs determined using eviQ and PBS data. Low rate of response to the Expert survey may have affected the generalisibility of the results - DHAP and brentuximab were the highest weighted comparator therapies, and the most expensive.	High, favours pralatrexate
Proportion of patients receiving SCT	Pralatrexate arm – derived from PDX-008 (■■■%) Comparator arm – derived from the Australian dataset (■■■%) Rates of SCT were calculated inappropriately by using the modelled probability of being alive at 27 weeks.	High, favours pralatrexate
Subsequent lines of treatment	In the base case the number of subsequent lines of treatment was set to zero, which was not realistic in light of the treatment algorithm and evidence from the Australian population.	High, favours pralatrexate

Source: Compiled during evaluation

ECOG = Eastern Cooperative Oncology Group; SCT = stem cell transplant

6.42. The results of the stepped economic evaluation are presented below.

Table 11: Results of the stepped economic evaluation

Step and component	Pralatrexate	Comparator	Increment
Step 1: PDX-008 versus international historical control cohort only; Cox regression model, stratified by cohort, used in both arms; 2 years			
Costs	\$████	\$████	\$████
Life years gained	████	████	████
Incremental cost/extra life year gained			\$████ per LY
Step 2: PDX-008 versus combined historical control cohort; Cox regression model, stratified by cohort, used in both arms; 2 years,			
Costs	\$████	\$████	\$████
Life years gained	████	████	████
Incremental cost/extra life year gained			\$████ per LY
Step 3: Clinical outcome data used; translation of study evidence to the Australian setting (Australian drug costs used); 2 years			
Costs	\$████	\$████	\$████
Life years gained	████	████	████
Incremental cost/extra life year gained			\$████ per LY
Step 4a: Application of health state utilities, chemotherapy administration costs and subsequent treatment costs			
Costs	\$████	\$████	\$████
QALYs gained	████	████	████
Incremental cost/extra QALY gained			\$████ per QALY
Step 4b: Step 4a and inclusion of AE costs and SCT costs			
Costs	\$████	\$████	\$████
QALYs gained	████	████	████
Incremental cost/extra QALY gained			\$████ per QALY
Step 5: 10 year time horizon			
Costs	\$████	\$████	\$████
QALYs gained	████	████	████
Incremental cost/extra QALY gained			\$████ per QALY
Results from November 2015			
Costs	\$████	\$████	\$████
QALYs gained	2.144	0.784	1.360
Incremental cost/extra QALY gained			\$████ per QALY
Results from March 2016			
Costs	\$████	\$████	\$████
QALYs gained	1.745	0.784	0.961
Incremental cost/extra QALY gained			\$████ per QALY

Source: Table 3.29, pp3-80 to 3-81 of the resubmission; and corrected during evaluation
 AE = adverse event; LY = life year; QALY = quality-adjusted life year SCT = stem cell transplant

- 6.43. When extrapolated to 10 years, the incremental cost effectiveness ratio (ICER) was at the lower end of the range of \$45,000 - \$75,000 per QALY gained (and \$15,000-\$45,000 per life year gained). As there was no additional accrual of costs or benefits past five years, when the survival curves converged, the ICER represented a five year time horizon.
- 6.44. This ICER was less than that presented in the November 2015 submission (\$45,000-\$75,000 per QALY) and in the March 2016 minor resubmission (\$45,000-\$75,000 per QALY). This reduced ICER, compared to the November 2015 submission, was largely driven by structural changes to the model to include post-progression treatment and stem cell transplants and their associated costs (appropriate), a reduction in the effective price of pralatrexate (appropriate) and a substantial increase in the cost of comparator treatment (not appropriate). The ICER was also influenced by the large difference in the rates of SCT between the two arms of the model, which were not appropriately calculated.
- 6.45. The ESC noted that subsequent lines of treatment were set to zero in the base case. Noting the resubmission's argument that pralatrexate was intended to be a last line therapy and patients would not receive any subsequent treatment, the ESC considered that this contradicted the treatment algorithm of R/R PTCL, and the evidence from the Australian patient population. The ESC noted that accounting for subsequent lines of therapy resulted in a considerable increase in the ICER.
- 6.46. The PBAC agreed with ESC that in practice pralatrexate may not be used last line, especially in patients who have to discontinue due to toxicity rather than progression. The pre-PBAC response arguments about whether the inclusion of subsequent therapies may reduce the ICER were noted. The PBAC considered that the applicability of the model's output to future clinical practice if the drug is subsidised is diminished by not including subsequent lines of therapy post pralatrexate.
- 6.47. This resubmission presented univariate, multivariate and probabilistic sensitivity analyses. The key univariate sensitivity analyses conducted by the resubmission and during evaluation are presented below.

Table 12: Results of the key univariate sensitivity analyses

	Incremental costs	Incremental effectiveness	ICER
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Structural issues			
No SCT following treatment or subsequent treatment	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Parameter changes			
Cost of pralatrexate (base case DPMA = \$ [REDACTED] per vial)			
+10% (\$ [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
-10% (\$ [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of comparator treatment (base case = \$ [REDACTED] per cycle)			
+ 10% (\$ [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
- 10% (\$ [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
\$ [REDACTED] (March 2016 resubmission)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
\$ [REDACTED] (November 2015 submission)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Comparator response rates (base case = [REDACTED]; i.e. same as pralatrexate and from PDX-008) CR = [REDACTED]; PR = [REDACTED]; SD = [REDACTED]; PD = [REDACTED] (from Australian historical database)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Lines of subsequent therapy (base case = 0)			
2	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
4	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
SCT rate in comparator arm (base case = 58.1%)			
[REDACTED]% (Treatment algorithm rate of pts in remission following 1 st -line therapy)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
[REDACTED]% (Treatment algorithm rate of pts in remission following 2 nd -line therapy)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utility changes			
Health state utilities (base case = Kang 2015: 0.885; 0.784; 0.746; 0.567) Swinburn 2012 (CR = 0.89; PR = 0.77; SD = 0.67; PD = 0.32)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3.34, p3-85; and Folutyn 2017 – Variables list (final).xlsx Excel spreadsheet; and calculated during evaluation
CR = complete response; DPMA = dispensed price for maximum amount; ICER = incremental cost-effectiveness ratio; PD = progressive disease; PR = partial response; pts = patients; SCT = stem cell transplant; SD = stable disease

6.48. The ESC noted that sensitivity analyses around areas of uncertainty generated ICERs that were considerably higher than the base case. The model was most sensitive to changes in the rate of stem cell transplant in the comparator arm, the cost of pralatrexate, the cost of the comparator and the lines of subsequent therapy received.

- The ESC noted that the resubmission assumed that all patients were eligible to receive a stem cell transplant after 27 weeks regardless of treatment success. The PSCR (p.4) stated that the 27 weeks was taken from the average amount of time between trial entry and SCT in PDX-008. The PSCR further claimed that given that such a large proportion of comparator arm patients are already dead by week 27 the probability of having an SCT (applied to those still alive) is appropriately adjusted such that the total number of SCT incurred by the entire

treatment cohort reflects clinical practice. However, the PSCR (p.4) acknowledged that given the data limitations, the model could not apply SCTs to only those simulated patients who respond to therapy, noting that doing so would not alter the associated mean costs nor would it lead to a change in the cohort average modelled life duration (it would only re-allocate this gain between responding and non-responding patients). The ESC considered that the differential SCT rates were uncertain, overstated and favoured pralatrexate (see 6.38);

- The ESC noted that the increase in comparator costs compared to the November 2015 submission was largely due to the increased cost attributed to DHAP, the most heavily weighted chemotherapy, through the inclusion of \$ [REDACTED] for concomitant filgrastim, the inclusion of the cost of brentuximab and the addition of vinorelbine to the cost of gemcitabine-containing regimens.
- The PBAC also considered that the cost of the basket of comparator drugs inappropriately included brentuximab. When excluded, the average cost of comparator drugs was reduced to \$ [REDACTED]. Changing the cost of the comparator alone increases the ICER to more than \$100,000/QALY gained.
- Overall, the ESC considered that although the economic model had structural improvements compared to previous submissions, the inputs were unreliable. Specifically, the uncertainty regarding the size of the OS difference and use of a stratified Cox regression model to estimate OS resulted in the possibility that survival was both overestimated in the pralatrexate arm, and underestimated in the comparator arm. The ESC therefore advised that any incremental cost-effectiveness of pralatrexate arising from this economic model is unreliable. The PBAC agreed, and considered that the model generated an optimistic estimate of the ICER. The PBAC considered a simpler model in which the incremental survival is calculated directly from the Kaplan Meier plots may be more informative, especially as no quality clinical data will arise to resolve the deficits in the existing data.

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

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

- 6.49. The total cost of pralatrexate treatment was calculated to be \$ [REDACTED], assuming a mean DPMA per vial of \$ [REDACTED] and 40.4 vials per patient, which was appropriately derived from individual patient data from study PDX-008). This represented a mean of [REDACTED] doses per patient or [REDACTED] cycles. The total cost of comparator treatment was \$ [REDACTED], assuming an average cost of comparator chemotherapy of \$ [REDACTED] and [REDACTED] cycles per patient. The PBAC considered the comparator costs to be substantially inflated due to the inappropriate inclusion of brentuximab.
- 6.50. In the November 2015 submission, the cost of pralatrexate was calculated to be \$ [REDACTED] per patient per course and the comparator cost \$ [REDACTED].

- 6.51. In the March 2016 minor resubmission, the cost of pralatrexate for an average patient using 42 vials is \$ [REDACTED] (\$ [REDACTED] x 42). There was no cost calculated for the comparator.

Estimated PBS usage & financial implications

- 6.52. This resubmission was not considered by DUSC.
- 6.53. This resubmission, as per the November 2015 submission, used an epidemiological approach to determine the likely number of patients and costs associated with listing pralatrexate on the PBS/RPBS. The March 2016 minor resubmission did not present full financial forecasts – it included a summary of costs to the PBS/RPBS that adjusted the number of vials per patient.
- 6.54. This resubmission updated the financial estimates. Individual patient data was used to calculate the average number of pralatrexate vials used per patient (40, rather than 32.9 in November 2015 and 35.2 in March 2016). This was appropriate. The weightings and costs of the comparator treatments were updated and costs associated with subsequent stem cell transplants were incorporated.
- 6.55. The rates of stem cell transplant used in the financial estimates (pralatrexate = [REDACTED]%; comparator therapy = [REDACTED]%) were not calculated appropriately and differed to those used in the economic model (pralatrexate = [REDACTED]%; comparator therapy = [REDACTED]%). This was inappropriate, not explained in the resubmission, nor tested in the sensitivity analyses.

Table 13: Estimated use and financial implications of pralatrexate ^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Nov 2015/Mar 2016	█	█	█	█	█	█
Number of prescriptions ^b	█	█	█	█	█	█
Nov 2015/Mar 2016 ^c	█	█	█	█	█	█
Estimated financial implications of pralatrexate						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Co-payments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for concomitant and replace therapies						
Cost of concomitant therapies to the PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost of replaced therapies to the PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to the PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
November 2015	\$ █	\$ █	\$ █	\$ █	\$ █	-
March 2016	\$ █	\$ █	\$ █	\$ █	\$ █	-
Net financial implications						
Net cost to MBS ^d	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to hospitals	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
November 2015	\$ █	\$ █	\$ █	\$ █	\$ █	-

Source: Folutyn Section 4 – Base Case 2017 (1 March).xlsx Excel spreadsheet; calculated during evaluation; Table 8, p18, November 2015 PBAC minutes; and Table 6, p15, March 2016 PBAC minutes

CT = computer tomography; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Differences due to rounding

^b Assuming █ prescriptions per patient. The resubmission assumed patients would receive █ prescriptions per patient, but as the average patient would commence █ cycles of therapy they would receive █ prescriptions. This resulted in errors in the co-payments.

^c The November 2015 and March 2016 submissions incorrectly assumed that patients would receive █ prescriptions per patient. The average patient would commence █ cycles of therapy and therefore receive █ prescriptions.

^d Number of CT scans corrected to 2. July 2017 resubmission assumed pralatrexate patients would receive █.

- 6.56. The number of patients treated with pralatrexate in the July 2017 resubmission was higher than estimated in November 2015. In year 5, the estimated number of patients was less than 10,000. This was primarily due to increases in the proportion of the PTCL population that was relapsed or refractory (from █% to █%) and the assumed uptake of pralatrexate (from █% to █%). The PBAC considered this number should be reduced by the number of patients receiving brentuximab for ALCL each year.
- 6.57. The net cost to the PBS/RPBS in Year 5 of the resubmission was \$30 – \$60 million. This was significantly higher than the estimates provided in the previous submissions (\$20 –\$30 million) due to the increase in the eligible patient population.

6.58. There was a high degree of uncertainty in the net cost to government, as it was dependent on a substantial reduction in the proportion of patients receiving subsequent stem cell transplants. The ESC considered that the magnitude and direction of differences in SCT rates were difficult to determine from the economic model and the financial estimates. The PBAC considered this would be a key component to establishing a cost-effective price for pralatrexate.

6.59. The key sensitivity analyses are presented below.

Table 14: Results of cost model sensitivity analyses

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
Net cost to PBS/RPBS						
Base case	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]
Price of pralatrexate (base = \$ [redacted]) + 10% (\$ [redacted]) - 10% (\$ [redacted])	\$ [redacted] \$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted] \$ [redacted]
% of NHL that is PTCL (base = 15%) 10% 5%	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]	\$ [redacted] \$ [redacted]
R/R PTCL (base = 68.8%) 52.5% (as per Nov 2015)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Uptake in PTCL (non-sALCL) patients (base: Yr 1: [redacted]% to Yr 6: [redacted]%) Yr 1: [redacted]% to Yr 6: [redacted]%	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to government						
Rate of SCT (base: Pral = [redacted]%, Comp = [redacted]%) [redacted]% and [redacted]% (per econ model) [redacted]% and [redacted]%	-\$ [redacted] \$ [redacted]	-\$ [redacted] \$ [redacted]	-\$ [redacted] \$ [redacted]	-\$ [redacted] \$ [redacted]	-\$ [redacted] \$ [redacted]	-\$ [redacted] \$ [redacted]

Source: Calculated during evaluation

Comp = comparator; NHL = non-Hodgkin lymphoma; PBS = Pharmaceutical Benefits Scheme; Pral = pralatrexate; PTCL = peripheral T-cell lymphoma; RPBS = Repatriation Pharmaceutical Benefits Scheme; R/R = relapsed or refractory; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant; Yr = year

Financial Management – Risk Sharing Arrangements

6.60. The resubmission requested a Special Pricing Arrangement such that the published ex-manufacturer price per 20 mg vial of pralatrexate was no less than \$ [redacted]. The resubmission proposed a risk share arrangement to alleviate any concerns the PBAC might have regarding eligible patient numbers. The pre-PBAC response (p.3-4) indicated that the sponsor was willing to enter into a risk share agreement to mitigate the uncertainties in the financial estimates.

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

7 PBAC Outcome

- 7.1. The PBAC did not recommend the Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL), on the basis of uncertainty about incremental clinical effectiveness over currently available alternative therapies, together with a high burden of AEs, and unacceptably high cost-effectiveness even if the clinical claim was accepted.
- 7.2. The PBAC recalled that the previous decisions to reject pralatrexate at the November 2015 and March 2016 had considered that a future major resubmission should present more robust evidence to demonstrate the comparative efficacy and safety of pralatrexate over the comparators, ideally including other evidence of clinical benefit, such as QoL data; and a substantially updated economic evaluation and revised financial estimates. Furthermore, noting that brentuximab for the treatment of adult patients with relapsed or refractory sALCL was accepted in the ICER range of \$45,000 to \$75,000/QALY, the PBAC had considered that given the uncertain clinical benefit of pralatrexate, an ICER at the lower end of this range would be needed in order for pralatrexate to be considered acceptably cost-effective. In the July 2017 resubmission, the PBAC noted these key considerations were not adequately met.
- 7.3. The PBAC recalled that it had considered that a second or later line listing as proposed in the resubmission was the appropriate clinical place for pralatrexate (paragraph 7.8, pralatrexate PSD, November 2015). The PBAC accepted that a basket of treatments was the appropriate main comparator, while noting that GND (gemcitabine, vinorelbine, doxorubicin) and romidepsin were appropriate comparators for the potential use of pralatrexate in the third line setting, after progression on brentuximab or other treatments from the submission's nominated basket of treatments in the second line. The PBAC advised that brentuximab was expected to remain the preferred choice of treatment for the sALCL subtype of PTCL and was most likely to be used prior to pralatrexate, as confirmed by the sponsor hearing for this resubmission, and therefore it was inappropriate to have included brentuximab in the nominated basket of comparators. This was reaffirmed by the fact that only one patient was treated with brentuximab in the evidence presented from historical control cohorts.
- 7.4. The PBAC noted that addressing the Committee's previous concerns regarding the method used in the matched controlled analysis to determine OS, this resubmission used a comparative analysis set of patients from the key single-arm, open label pralatrexate study PDX-008 (N = 115), and a combined historical cohort consisting of data from four international (N = [REDACTED]) and one Australian (N = [REDACTED]) control cohorts. The PBAC noted that the treatments received by patients in the historical control cohort were not representative of the nominated basket of comparator treatments, given that approximately [REDACTED]% of patients from the international database had not

received a therapy from the basket of comparator treatments as their most recent therapy.

7.5. The PBAC maintained that the clinical evidence presented in the resubmission was insufficient in establishing a meaningful survival benefit, as:

- key confounders, particularly prognostic factors such as LDH, extranodal disease, stage, presence or absence of B symptoms, were imbalanced across the three patient cohorts;
- OS in the combined historical control cohort (■■■ months (95% CI: 4.1, ■■■)) underestimated the median OS for patients with PTCL in Australia;
- the Australian control cohort, although clinically relevant, was small, and therefore any comparisons conducted were statistically underpowered and unreliable.

7.6. The PBAC noted the pre-PBAC response on the above issues, including the arguments against the relevance of the potential confounding factors identified by ESC (except for performance status). Nevertheless, the fundamental flaw in the data presented remains – the submission compares outcomes of patients prospectively accrued into a clinical trial requiring strict entry criteria and who could receive further lines of therapy after pralatrexate, with patients treated non-contemporaneously and without strict entry criteria, and only using data from their last line of therapy. This confounding cannot be overcome fully, neither by approaches taken in the current resubmission, nor the matched analysis used previously. The PBAC therefore considered that the survival benefit has not been proven and that the incremental clinical benefits are highly uncertain. The submission's claim of superior comparative effectiveness against the nominated basket of treatments remained unsupported.

7.7. The PBAC considered that pralatrexate had a different safety profile compared to the resubmission's nominated basket of treatments, noting the high burden of AEs in the PDX-008 study that included mucosal inflammation (68%), nausea (33%), fatigue (30%), thrombocytopenia (40%), leading to 23% treatment discontinuations as a result of AEs. The PBAC also noted the pre-PBAC response (p.2) claimed that pralatrexate did not demonstrate any significant cumulative toxicity, nor any adverse impact on QoL, making it suitable for longer term therapy¹. The PBAC noted the lack of QoL data to provide support for the claim of improved tolerability. The PBAC noted that 20.7% of patients treated with pralatrexate experienced Grade 3 or 4 mucositis which represents major morbidity; that 23% of patients discontinued due to AEs, and that 1.2% (95% CI 0.2, 5.5%) of patients died of toxicity. The PBAC agreed that safety was non-inferior to other chemotherapy regimens, but that the rates of severe mucositis and discontinuations due to adverse events were substantial and indicated that the treatment had significant toxicity.

¹ Ther Adv Hematol. 2013 Jun;4(3):173-87. doi: 10.1177/2040620713481980.

7.8. The PBAC recalled that in its November 2015 consideration of pralatrexate, the Committee had considered that the economic evaluation was neither informative nor meaningful, given the clinical evidence did not support the clinical claim (paragraph 7.6, pralatrexate PSD, November 2015). The PBAC noted that several structural improvements were incorporated in the economic model presented in this resubmission, however:

- OS for pralatrexate patients was overestimated (■■■■ months) in the economic model, when compared to results from PDX-008 (14.7 months);
- The comparator costs presented in the economic model in this resubmission was \$■■■■, which was higher than comparator costs of \$■■■■ and \$■■■■ from the November 2015 and March 2016 submissions, respectively. The PBAC noted that this was due to the inclusion of DHAP and brentuximab, which were the highest weighted, and most expensive, comparator therapies. The PBAC further noted that comparator cost was a key driver of the model, and highly favoured pralatrexate, as the removal of brentuximab and adjusting for the comparator response rates provided in the PSCR (p.4) resulted in an ICER of \$105,000/QALY – \$200,000/QALY;
- Although the relative proportion of patients receiving SCT at 27 weeks were assumed to be ■■■% and ■■■% for the comparator and pralatrexate arms respectively, these rates differed again to those applied in the financial estimates (■■% and ■■%). The PBAC considered that the differences in rates of SCT between the two arms could likely reflect the different intents of therapy in this non-randomised comparison, again emphasizing the inherent uncertainty in the approach;
- The number of subsequent lines of treatment was assumed to be zero. The PBAC considered that this contradicted the treatment algorithm of R/R PTCL, and the evidence from the Australian patient population, noting that accounting for subsequent lines of therapy resulted in a considerable increase in the ICER; and
- The PBAC noted that the price of pralatrexate was unchanged from the March 2016 resubmission.

7.9. Overall, the PBAC considered that the underlying lack of evidence to support the claim of superior efficacy resulted in unreliable inputs and optimistic extrapolations, leading to an economic model that did not provide a plausible estimate of the cost-effectiveness of pralatrexate. As such, notwithstanding the clinical need for new and effective treatments for relapsed or refractory PTCL, the PBAC remained unconvinced that pralatrexate was cost effective compared to current treatments available to patients, at the price proposed by the submission.

7.10. The PBAC noted that the net cost to the PBS was highly variable as it was dependent on the proportion of patients receiving post-treatment stem cell transplant, creating uncertainty in the estimation of the uptake of pralatrexate in the proposed PBS

population. The PBAC noted that the pre-PBAC response (p3) indicated the sponsor's willingness to enter into a risk share agreement with the Department in order to mitigate the uncertainties regarding the financial estimates.

- 7.11. The PBAC reiterated any future major resubmission should include more conservative assumptions that include a lower SCT rate in the comparator arm than the pralatrexate arm, noting that Australian data indicated that this was approximately █%; at least two lines of subsequent therapy; and the removal of brentuximab from the cost-offsets, along with a substantial price reduction, to account for the associated uncertainty in the incremental clinical benefit. The PBAC advised that an economic model incorporating these assumptions and an ICER at the lower end of \$45,000 to \$75,000/QALY (the range in which brentuximab for sALCL was considered cost-effective) would be necessary in order for pralatrexate to be acceptably cost-effective.
- 7.12. The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

As recognised by the PBAC, there is a clinical need for new effective treatments for the relapsed or refractory peripheral T-Cell lymphoma. Mundipharma remains committed to making pralatrexate available to patients with relapsed or refractory peripheral T-Cell lymphoma.