

5.13 PRALATREXATE, solution for infusion, 1 mL vial, 20mg, Folotyn[®], Mundipharma Pty Ltd.

1 Purpose of Application

- 1.1 Section 100, Authority Required, listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of repeats	Published DPMA	Effective DPMA	Proprietary Name and Manufacturer
PRALATREXATE Pralatrexate 20mg in 1mL, solution for infusion (public hospital)	80mg	5	\$ [REDACTED]*	\$ [REDACTED]*	Folotyn® Mundipharma
PRALATREXATE Pralatrexate 20mg in 1mL, solution for infusion (private hospital)	80mg	5	\$ [REDACTED]*	\$ [REDACTED]*	Folotyn® Mundipharma

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

Category / Program	Chemotherapy (Private and Public)
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
Episodicity:	<i>Peripheral T-cell Lymphoma</i>
Severity:	Patients who have relapsed or chemotherapy refractory disease
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	<i>Relapsed or chemotherapy refractory peripheral T-cell Lymphoma</i>
Treatment phase:	Initiation -Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Patient must demonstrate relapsed or chemotherapy refractory disease to 1st line chemotherapy.

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Clinical criteria:	<p>Patient must have undergone appropriate prior front-line curative intent chemotherapy</p> <p>AND</p> <p>Patient must demonstrate relapsed or chemotherapy-refractory disease</p>
Population criteria:	Adults
Prescriber Instructions	<p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed PTCL Pralatrexate PBS Authority Application - Supporting Information Form [to be determined] which includes the following:</p> <p>(i) The date of initial diagnosis of PTCL;</p> <p>(ii) Dates of commencement and completion of front-line curative intent chemotherapy;</p> <p>(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</p> <p>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).</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Note</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Note</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Note</p> <p>Special Pricing Arrangements apply.</p>

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Max. Qty	Price for	Proprietary Name and Manufacturer
PRALATREXATE, 20mg in 1 mL, solution for infusion	80 mg	11	\$ [REDACTED]	(public) (private)	Folotyn Mundipharma

Category / Program	Chemotherapy (Private and Public)
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
Episodicity:	Peripheral T-cell Lymphoma
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
Treatment criteria:	Patient must demonstrate relapsed or chemotherapy refractory disease to 1st line chemotherapy.
Clinical criteria:	Patient must not have progressive disease, And Patient must have previously been issued with an authority prescription for this drug.
Prescriber Instructions	
Administrative Advice	Note <i>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).</i> 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 requested listing (treatment in second line) is inconsistent with the clinical evidence presented in Section B of the Commentary. Patients in the primary study in Section B (PDX-008) had a median of 3 lines prior therapy. This was not explored in Section C of the submission.
- 2.2 The requested basis for listing is cost-effectiveness compared with the nominated comparator.

3 Background

- 3.1 TGA status: Pralatrexate was approved by the TGA in January 2015 for adult patients with peripheral T-cell lymphoma who have progressed after at least one prior therapy. The ARTG entry date is 11 August 2015
- 3.2 Pralatrexate has not been considered by the PBAC previously.

4 Clinical place for the proposed therapy

- 4.1 Peripheral T-cell lymphoma (PTCL) comprises a group of heterogeneous non-Hodgkin lymphomas that develop from T-cells in different stages of maturity. The sub-types of lymphoma that are categorised as PTCL in the submission are (pA26 of the submission):
- Peripheral T-Cell Lymphoma (Not Otherwise Specified - NOS)
 - Anaplastic Large-Cell Lymphoma (ALCL)
 - Angioimmunoblastic T-cell lymphoma
 - Primary cutaneous PTCL (primary cutaneous gamma delta T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoma, and primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, Mycosis Fungoides (cutaneous T-cell Lymphoma) and Sézary Syndrome (cutaneous T-cell Lymphoma))
 - Enteropathy-associated T-Cell Lymphoma (involvement of celiac)
 - Hepatosplenic Gamma-Delta T-Cell Lymphoma
 - Blastic NK-cell lymphoma
 - Adult T-cell acute Lymphoblastic Leukemia/Lymphoma T-Cell Leukemias
 - Subcutaneous panniculitis-like T-cell Lymphoma
 - Extranodal NK (natural killer/T-cell lymphoma) - Nasal T-Cell Lymphoma
 - Precursor T-Cell Acute Lymphoblastic Lymphoma or Leukaemia
- 4.2 It is proposed that pralatrexate will be administered in the second line for treatment of PTCL.

5 Comparator

- 5.1 The submission nominated a basket of treatments as the main comparator. The basket of treatments included DHAP, brentuximab, gemcitabine containing regimens, methotrexate, romidepsin (not PBS listed in Australia), ESHAP, and ICE. The ESC considered that this basket is 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 comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission is based on a naïve comparison of
- Pralatrexate: Study PDX-008 (n=█). A sub-group of patients from Study PDX-008 (n=█) was matched to a historical control cohort.
 - Comparator treatments: Matched control analysis (MCA). A subset of patients from PDX-008 were matched *on a 1:1 basis* to a historical control cohort (n=█).
- 6.4 PDX-008 was a Phase 2, single-arm, open-label multi-centre study conducted in US, Canada and Europe for patients with relapsed or refractory PTCL. █ patients were recruited, and █ patients formed the efficacy evaluable population (received at least 1 dose of pralatrexate and histology was confirmed by central review).
- 6.5 The historical control cohort consisted of █ patients that were consistent with the main PDX-008 inclusion criteria (█) were extracted.
- 6.6 Each PDX-008 patient (n=█), for whom a match could be obtained, was matched to multiple control patients (n=█). Patients were matched on the basis █. Patients were not matched on the basis █.
- 6.7 Each PDX-008 patient (n=█) was matched with █
- 6.8 Patients with a 1:1 match were identified as a case match. Where cases had multiple control matches the control match was randomly selected. The total matched population was █ cases and █ controls.
- 6.9 Further details of the studies presented in the submission are provided in the table below.

Table 1: Studies and associated reports presented in the submission

Study	Description	Reports
Pralatrexate		
<i>Nonrandomised studies</i>		
PDX-008	Single arm, Phase 2 study evaluating efficacy and safety of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma	<p>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</p> <p>O'Connor, O. A., B. Pro, L. Pinter-Brown, N. Bartlett, L. Popplewell, B. Coiffier, M. J. Lechowicz, K. J. Savage, A. R. Shustov, C. Gisselbrecht, E. Jacobsen, P. L. Zinzani, R. Furman, A. Goy, C. Haioun, M. Crump, J. M. Zain, E. Hsi, A. Boyd and S. Horwitz. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. <i>Journal of clinical oncology: official journal of the American Society of Clinical Oncology</i>, 2011, 29(9): 1182-1189.</p> <p>O'Connor, O., P. L. Zinzani, T. Koutsoukos and B. Coiffier. Pralatrexate reverses the trend in progressive resistance with successive chemotherapy regimens in the treatment of relapsed or refractory peripheral t-cell lymphoma (PTCL). <i>Haematologica</i>, 2011, 96: 151-152.</p> <p>Foss, F. M., S. M. Horwitz, L. Pinter-Brown, A. Goy, B. Pro, B. Coiffier, L. Popplewell, K. J. Savage, A. Shustov, J. M. Zain, T. Koutsoukos, S. M. Fruchtman and O. A. O'Connor. Pralatrexate is an effective treatment for heavily pretreated patients with relapsed/refractory transformed mycosis fungoides (TMF). <i>Blood</i>, 2010, 116(21).</p> <p>Goy, A., B. Pro, K. J. Savage, N. L. Bartlett, M. J. Lechowicz, E. D. Jacobsen, F. Young, M. Crump, H. Borghaei, B. Link, S. M. Fruchtman and O. A. O'Connor. Pralatrexate is effective in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with prior ifosfamide, carboplatin, and etoposide (ICE)-based regimens, 2010, <i>Blood</i> 116(21).</p>
Main comparator		
Matched controls analysis	Individual patient historical control data matched to patients in PDX-008	Allos Therapeutics Ltd. Historical Controls Data Report, including Attachments. August 2013

Source: Table B.2.2, p B13 of the submission

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

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pralatrexate						
PDX-008	111	OL, MC, single arm 2yrs (up to 5 years for some patients)	High	Progressive disease after at least 1 prior treatment	ORR, OS, PFS	Survival
Pralatrexate vs comparator						
MCA	■	Historical database patients matched 1:1 to PDX-008	High	■	■	■

MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; ORR=overall response rate, MCA=matched control analysis

Source: compiled during the evaluation

6.11 The following issues were identified with regards to the study design:

- PDX-008 was a single arm study, without a comparator or randomisation and is therefore subject to considerable bias.
- Overall survival in the sub-group representing the matched cohort in PDX-008 was ■ months compared to ■ months in the overall efficacy evaluable population. It is possible that the matched population represent a healthier population than the overall efficacy evaluable population, biasing the hazard ratio in favour of pralatrexate.
- Patients in PDX-008 were not matched to historical controls on the basis of ECOG status. Given an inclusion criteria of PDX-008 was ECOG ≤ 2 it is likely that PDX-008 patients have a better performance status than the matched historical controls. Performance status is a predictive factor of improved outcomes so this has the potential to bias in favour of pralatrexate.
- The PSCR (p30) noted that the majority of patients with known ECOG performance status in the historical control cohort were ≤ 2, and would be willing to restrict the indication to this group.
- The ESC were concerned that the incremental survival of ■ months for pralatrexate compared to historical controls (■ vs ■ months) appeared implausible when the median PFS for pralatrexate was only 3.5 months.
- The recruitment periods for the historical controls (■) were older than that of PDX-008 (2006-2008). Survival outcomes in those recruited in later time periods may be improved due to advances in treatment options, advances in supportive care and the increasing use of stem cell therapy. The PSCR (p3) argued that the comparison was valid because there was significant overlap between the 2 cohorts, and cited a study of 153 patients (Mak JCO 2013) that did not find difference in survival rates for patients with PTCL not undergoing transplant treated 1980-2000 vs 2001-2011. However, the ESC remained concerned that differences in overall survival between pralatrexate and the comparators were highly uncertain and likely over-estimated.
- The submission presented 2 sensitivity analyses using different matching methodologies. The hazard ratio was sensitive to the matching methodology employed. The hazard ratio for overall survival in the base case was ■ (95%CI: ■, ■) compared to ■ (95%CI: ■, ■) and ■

(95%CI: [REDACTED], [REDACTED]) in the sensitivity analyses.

Comparative effectiveness

6.12 Original results in PDX-008 were based on a follow-up period of 2 years post pralatrexate initiation. Updated survival data were obtained for [REDACTED] patients in the efficacy evaluable population of which [REDACTED] patients were in the matched PDX-008 cohort. Those patients for whom updated data were not received were censored at two years. Of those [REDACTED] patients, there were [REDACTED] deaths and the remaining [REDACTED] were censored [REDACTED]. The tail of the Kaplan-Meier curve for pralatrexate suggests a low death rate beyond [REDACTED] months however the incremental benefit should be interpreted with caution due to the small patient numbers and high rates of censoring. Furthermore, it is unknown whether the patients for whom updated data are received are representative of the overall efficacy population.

Table 3: Results of overall survival and progression free survival in the non-randomised studies

	PDX-008 N=109 (original results)	PDX-008 N=109 (updated* results)	Matched PDX-008 cohort N=66 (based on updated* results)	Matched historical control cohort N=66	Absolute difference	Hazard ratio (matched PDX-008 and matched historical control cohort)
Median PFS (95%CI)	3.5 (1.7-4.8)	NR	NR	NR	NR	NR
Median OS (95%CI)	14.5 (10.6- 22.5)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Table B.6.2, p B66, Figure B.6.3, pB79 of the submission and page 37 of clinical-overview-row.pdf

Abbreviations: CI – Confidence interval, OS – Overall survival, PFS – Progression free survival, NR – Not reported

*Updated results based on additional survival data obtained from [REDACTED] patients in the overall trial population. Additional survival data was up to a four year follow-up period

Figure 1: Overall survival for matched PDX-008 (updated results) versus control matched patients



- 6.13 The PSCR (p1) acknowledged that 3 and 4 year data is based on small patient numbers, but did not provide numbers at risk for the Kaplan Meier survival curve, nor additional data to support the sponsor's assertion that such patients are representative.

Supportive evidence from study PDX-008 and a meta-analysis of fourteen single arm comparisons, utilising a variety of combination therapies examining refractory and or relapsed PTCL patients, indicated that the overall response rate for pralatrexate was not improved compared to brentuximab or the combination therapies, as acknowledged by the PSCR.

Figure 2: Overall response rate to pralatrexate, single agent (brentuximab) and combination regimens



The redacted figure above shows the primary measurement for the overall response rate for pralatrexate was 29% (95% CI 21, 39%) which was compare with brentuximab, gemcitabine, DHAP, ESHAP, ICE and mixed pool analysis.

- 6.14 The ESC noted that the submission stated that pralatrexate had comparable efficacy to other single-agent regimens such as brentuximab (B.6.4.1 of the submission).

Comparative harms

- 6.15 The submission did not present a comparative safety analysis of pralatrexate and comparator treatments, sourced from randomised studies. It was acknowledged that there is little adverse event information published from RCTs about chemotherapy combinations. Patients in PDX-008 experienced a high burden of adverse events. Notably, 25% of patients had at least one serious adverse event that was treatment-related and 23% of patients in PDX-008 discontinued treatment due to adverse events. In PDX-008 the most commonly reported treatment-related adverse events were mucosal inflammation (68%), thrombocytopenia (40%), nausea (33%), anaemia (32%), fatigue (30%), neutropenia (24%) and epistaxis (23%). Nausea, anaemia, fatigue and epistaxis were generally mild in severity. Mucosal inflammation was common amongst patients and 22% of patients experienced Grade 3 or 4 mucosal inflammation. 31% of patients experienced grade 3-4 thrombocytopenia and 21% of patients experienced grade 3-4 neutropenia.

Benefits/harms

- 6.16 A summary of the comparative benefits and harms for pralatrexate versus the comparator is presented in the table below.

Table 4: Summary of comparative benefits and harms for pralatrexate and comparator

MCA	Pralatrexate (PDX-008 matched cohort n=■)^	Comparator	Absolute Difference	HR (95% CI)		
OS (median months)	19.0 (11.4,NE)	■	■	■		
Harms						
	Pralatrexate	Comparator	RR (95% CI)	Event rate/100 patients/ per 2 years		RD (95% CI)
				Pralatrexate	Comparator	
Treatment related neutropenia (all grades)						
PDX-008 efficacy evaluable population	27/111	NR	NE	■	NR	NE
Treatment related thrombocytopenia (all grades)						
PDX-008 efficacy evaluable population	44/111	NR	NE	■	NR	NE
Treatment related mucosal inflammation (all grades)						
PDX-008 efficacy evaluable population	76/111	NR	NE	■	NR	NE

Source: Table B.6.2, p B66, Figure B.6.3, pB79 of the submission and page 37 of clinical-overview-row.pdf

Abbreviations: OS = overall survival, HR= hazard ratio, NR = not reported, NE = not evaluable, MCA = matched control analysis

^ Based on updated results; additional survival data obtained from ■ patients in the efficacy evaluable population and ■ patients in the matched population

- 6.17 On the basis of the naïve comparison of pralatrexate and the comparator, there was approximately [REDACTED] months difference in overall survival. The ESC considered this survival benefit was likely over-estimated.
- 6.18 The difference in adverse events between pralatrexate and the comparator is unknown. The PSCR (p1) argues that pralatrexate has a more tolerable toxicity profile than the comparators, allowing responders to pralatrexate to continue therapy over a longer period extending disease control, but did not present additional data to support this assertion.

Clinical claim

- 6.19 The submission described pralatrexate as superior in terms of comparative effectiveness over single-agent and combination therapies. In terms of comparative safety the submission described pralatrexate as non-inferior to single agent regimens and superior to combination regimens. The ESC considered that claim for efficacy and safety was not adequately supported:
- The key study presented in the submission (PDX-008) is a non-randomised, single arm, open-label study. As such, the study is subject to considerable bias and the effectiveness estimates are subject to considerable uncertainty.
 - The submission presented a naïve comparison of a matched sub-group of PDX-008 to a matched historical control cohort selected from 4 international lymphoma databases. The comparison is conducted by performing a 1:1 matched control analysis. Alternate approaches to conducting the matched controls analysis highlighted that the hazard ratio is sensitive to the matching methodology employed.
 - The matched sub-group (n=[REDACTED]) in PDX-008 had a higher median overall survival (OS) ([REDACTED]) compared to the efficacy evaluable population (n=[REDACTED]) ([REDACTED]). This has the potential to bias the overall hazard ratio in favour of pralatrexate.
 - Patients were not matched on the basis of [REDACTED], [REDACTED]. An inclusion criterion of PDX-008 was an ECOG status of 2 or less. It is likely that PDX-008 patients have, on average, a better performance status than patients extracted from the databases. This has the potential to bias survival outcomes in favour of the treatment group.
 - The submission did not present a comparative safety analysis of pralatrexate compared to comparator treatments.
- 6.20 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.21 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.22 **Table 5: Summary of model structure and rationale**

Time horizon	10 years in the model base case versus 5 years in trial
Outcomes	Life years, deaths and QALYs
Methods used to generate results	Markov model with Monte Carlo simulation
Health states	Patients were modelled as alive or dead. Alive patients were partitioned into complete response, complete response (unevaluable), partial response, stable disease, progressive disease and unevaluable response.
Cycle length	One month
Transition probabilities	Parametric function is used to approximate the matched historical control cohort reference overall survival curve with the hazard ratio applied to approximate the overall survival curve in the pralatrexate arm. Proportion of patients in each alive health state assumed to be equal in each arm. Derived from PDX-008.

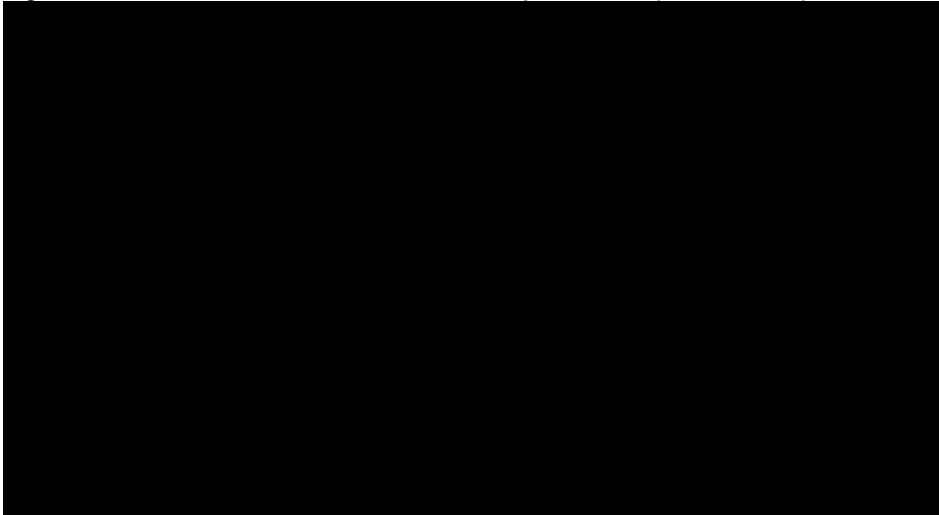
Source: constructed during the evaluation

6.23 The ESC noted that the Commentary had identified a number of technical issues with the model, including:

- All costs seem to be included as one off costs up front (hence the pralatrexate arm costs do not change from Step 2b onwards in the 'stepped economic evaluation' table below, even with discounting and a change in model time horizon), rather than accruing over time with treatment. The ESC considered this lead to implausible results that favour pralatrexate, whereby incremental costs for 5 years and 10 years follow up are identical, so incremental costs are not increasing over time, even though patients continue to accrue health outcomes.
- No variation of proportion of patients in each response state across treatment arms or with cycle. This result in the QALYs being driven by survival, rather than any changes in response to treatment.
- No inclusion of post-progression treatment costs and consequences, including stem cell transplant. The ESC disagreed with the PSCR (p5) when the response claimed that inclusion of these costs would define the resulting analysis as a 'cost of illness study'.
- Modelled overall survival estimates in the TreeAge economic model are inconsistent with the Kaplan Meier data. Survival estimates from the economic model show that █% of patients in the matched control cohort are alive after █ years and █% of patients in the matched control cohort are alive at the end of the model. █% of patients in the matched pralatrexate cohort are alive after █ years and █% of patients in the matched pralatrexate cohort are alive at the end of the model. These estimates are inconsistent with the Kaplan-Meier data (█ year survival of █% in the matched control cohort and █% in the matched PDX-008 cohort). In addition, the model estimates that █% of pralatrexate patients and █% of matched cohort patients are alive at █ years. The PSCR (p2) identified an error in the model that resulted in a modelled overall survival that is longer than would be anticipated from the Kaplan-Meier curves. The corrected model indicated that in the pralatrexate arm █% of patients are still alive and in the comparator arm █% of patients are still alive at the end of the model. After █ years, █% of patients in the pralatrexate arm are still alive and █% of patients in the comparator arm are still alive. Despite correction in the revised model provided in the PSCR, the ESC considered that incremental survival was still overestimated in the model. Based on the information in the

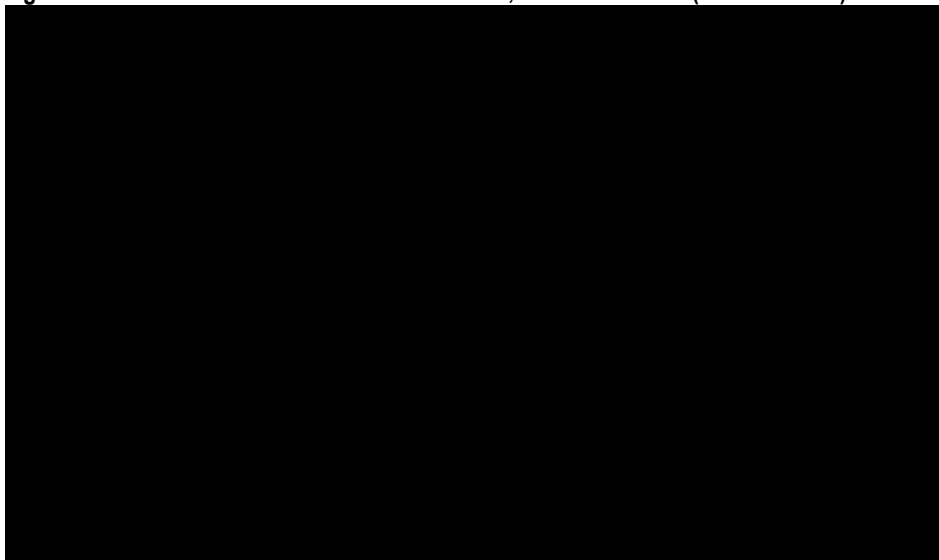
submission, this inconsistency can be visualised by comparing the Kaplan Meier data and Markov traces (pralatrexate and control arms) from the model in the figures below.

Figure 3: Overall survival in the economic model; pralatrexate (Markov Trace)



Source: Figure C(i).2.1 of the Commentary. Extracted during the evaluation from the economic model (Folotyn Model FINAL (Step 5) Base Case.trex)

Figure 4: Overall survival in the economic model; matched cohort (Markov Trace)



Source: Figure C(i).2.2 of the Commentary. Extracted during the evaluation from the economic model (Folotyn Model FINAL (Step 5) Base Case.trex)

Figure 5: Overall survival; Kaplan Meier curves and log-logistic parametric curve



6.24 Table 6: Key drivers of the model

Description	Method/Value	Impact
Hazard ratio	█ (matched control analysis)	High, favours pralatrexate
Dose of pralatrexate	Calculated based on mean total dose in PDX-008. Does not include wastage	High, favours pralatrexate
Cost of comparator chemotherapy regimens	Based on chemotherapy treatments in the matched historical control cohort (not include brentuximab)	Low, favours comparator
Utility values	Swinburn 2012	Moderate, favours pralatrexate
Costs of adverse events	Treatment related to neutropenia included, other adverse events excluded	Low
Choice of parametric function	Log-logistic	Low

Source: compiled during the evaluation

6.25 Table 7: Results of the stepped economic evaluation

Step and component	Pralatrexate	Comparator	Increment
Step 1: Trial-based outcomes			
Life years			
Incremental cost/extra outcome gained			NA
Step 2a: Trial based costs and outcomes (pralatrexate and comparator drug costs)			
Costs	\$		\$
Life years			
Incremental cost/life year gained			\$ /LYG
Step 2b: Trial based costs and outcomes (pralatrexate and comparator drug costs, co-medication, admin and adverse event costs)			
Costs	\$		\$
Life years			
Incremental cost/life year gained			\$ /LYG
Step 3a: Inclusion of utilities			
Costs	\$		\$
Life years			
QALYs			
Incremental cost/life year gained			\$ /LYG
Incremental cost/QALY gained			\$ /QALY
Step 3b: Inclusion of discount rate			
Costs	\$		\$
Life years			
QALYs			
Incremental cost/life year gained			\$ /LYG
Incremental cost/QALY gained			\$ /QALY
Step 4: Replacement of Kaplan-Meier curves with parametric curve for matched historical cohort and hazard rate applied to pralatrexate arm			
Costs	\$		\$
Life years			
QALYs			
Incremental cost/life year gained			\$ /LYG
Incremental cost/QALY gained			\$ /QALY
Step 5: Modelled evaluation: model extended to 10 years			
Costs	\$		\$
Life years			
QALYs			
Incremental cost/life year gained			\$ /LYG
Incremental cost/QALY gained			\$ /QALY

Source: Table D.6.1, pD31, Table D.6.2, pD33, Table D.6.3, pD35 of the submission

6.26 The Kaplan-Meier estimates in the economic model were not able to be verified during the evaluation. The source of the estimates used in the pralatrexate arm was not able to be identified during the evaluation. In the comparator arm the Weibull survival curve was used instead of the Kaplan Meier curve. As a result the ICERs up to Step 3b are unable to be verified. The ESC noted that the PSCR indicated the estimates used were derived from the matched cohort report, however, the ESC could not identify the data in the sources stated in the PSCR to verify these estimates.

- 6.27 The PSCR (p2) corrected errors in the model, including the mortality estimates. The PSCR updated the base case ICER to be \$45,000/QALY – \$75,000/QALY.
- 6.28 The submission presented univariate and probabilistic sensitivity analyses. The evaluation conducted additional univariate sensitivity analysis to examine the impact of wastage, not considered by the submission. Including wastage the ICER increased to \$75,000/QALY – \$105,000/QALY.
- 6.29 The evaluation also explored the impact of using the alternate hazard ratios obtained in the sensitivity analyses of the matched controls analysis (MCA). This was considered important as the hazard ratio was sensitive to the matching methodology employed. Using these alternate hazard ratios the ICER increased to \$75,000/QALY – \$105,000/QALY.
- 6.30 The model was most sensitive to the dose (number of vials) of pralatrexate and the incremental survival gain.

Drug cost/patient: \$ [REDACTED]

- 6.31 The total cost of treatment was modelled to be \$ [REDACTED]. This was based on the total dose of treatment in PDX-008, an assumed body surface area (assumed separately for males and females, 1.8m² overall) and a gender ratio obtained from the matched control cohort. Based on the mean number of cycles in PDX-008 (3 cycles) the cost per cycle was \$ [REDACTED]. The total cost of treatment of the comparator was modelled to be \$ [REDACTED] (this cost was based on the basket of comparator therapies nominated in the clinician survey). Based on an average of [REDACTED] cycles the cost per cycle was \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.32 This submission was not considered by DUSC. The submission adopted an epidemiological approach. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$20 – \$30 million million.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	■	■	■	■	■
Market share (sALCL patients)	20%	30%	30%	30%	30%
Market share (all other patients)	■%	■%	■%	■%	■%
Scripts*	■	■	■	■	■
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■
Net cost to MBS	■	■	■	■	■
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$■	\$■	\$■	\$■	\$■

Source: Table E.3.2, pE11 of the submission, Table E.6.3, pE38 of the submission, Folutyn – Section E Base Case (Ver10).xlsx, sheet Net Cost to PBS

*Assuming 14 scripts per person as estimated by the submission.

Abbreviations. sALCL - Systemic Anaplastic Large Cell Lymphoma.

- 6.33 The 6th Community Pharmacy Agreement which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.

In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

- The preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed;
- The preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at \$102.67* (indexed price for 2014/2015);
- The preparation fees paid to a s90 Community Pharmacy (including s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines;
- The preparation fee paid to non-TGA licensed compounders is \$20 less at \$82.67.
- Where applicable, the \$20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA); and.
- The \$20 is not currently captured by the DMPA that is published in the Schedule of Pharmaceutical Benefits.

As the majority of chemotherapy preparations are compounded in settings where the \$102.67 fee applies, this fee should continue to be used in PBAC submissions.

- 6.34 There is potential for the net cost to government to be greater than the estimate in the submission given that:
- The number of patients receiving treatment for PTCL in second line may grow.

- The estimated total number of vials per patient has been calculated incorrectly by the submission.
- The submission does not consider the number of vials administered per dose (i.e. wastage).
- The special pricing arrangements for brentuximab results in a reduced offset due to patients not using brentuximab.

Financial Management – Risk Sharing Arrangements

- 6.35 The submission requested a Special Pricing Arrangement such that the pricing of pralatrexate be published at no less than \$ [REDACTED] (ex. man - per 20mg vial). The submission proposed a risk share arrangement so that any additional cost to government as a result of a Special Pricing Arrangement is rebated to government.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma. In reaching this conclusion, the PBAC considered that there was insufficient evidence of the incremental clinical benefit against currently available treatments, concerns regarding a high burden of adverse events, and economic modelling was not reliable to enable the Committee to determine the cost-effectiveness of the pralatrexate in the Australian context.
- 7.2 The PBAC accepted that the basket of treatments was the appropriate the main comparator.
- 7.3 The PBAC noted that the PDX-008 trial of pralatrexate was a single arm study, which by its nature is subject to biases. The PBAC recalled that other submissions, including brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, have utilised a matched cohort analysis to quantify the comparative clinical efficacy of treatments in small patient populations. While the PBAC considered that this analysis was appropriate, the Committee was concerned 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 (median survival of 19 and [REDACTED] months respectively). The PBAC noted that the hazard ratio for overall survival in the base case matched controls analysis (MCA) was [REDACTED] (95%CI: [REDACTED], [REDACTED]) while using different matching methodologies, hazard ratio was [REDACTED] (95%CI: [REDACTED], [REDACTED]) and [REDACTED] (95%CI: [REDACTED], [REDACTED]).
- 7.4 The PBAC considered that there is a clinical need for new effective treatments for the relapsed or refractory peripheral T-Cell lymphoma, and noted that this view was reiterated in the pre-PBAC response. The PBAC considered that there was insufficient evidence of incremental benefit of pralatrexate versus comparators, based on evidence from study PDX-008, in which median progression-free survival was 3.5 months, and a meta-analysis of fourteen single arm comparisons indicated that the overall response rate for pralatrexate was not improved compared to

brentuximab or combination therapies. Overall, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data in the submission.

- 7.5 The PBAC noted study PDX-008 was associated with high burden of adverse events, where 25% of patients had ≥ 1 treatment-related serious adverse event, 23% of patients in PDX-008 discontinued treatment due to adverse events. The PBAC noted the discussion of comparative safety by the sponsor in the PSCR and the pre-PBAC response, but considered that the evidence presented in the submission did not support the claim of claim of non-inferior comparative safety in the submission.
- 7.6 The PBAC agreed with the ESC that there was insufficient clinical evidence to support the claim of superior efficacy and non-inferior safety, and therefore considered the economic evaluation presented in the submission was neither informative nor meaningful. The PBAC noted that, as presented in the submission, the ESC considered that the model was not sufficiently reliable to provide a plausible estimate of value for money for the listing of pralatrexate. The PBAC noted that of the many issues raised by ESC, the pre-PBAC response only addressed the issue of post-progression costs, which reiterated that these costs should not be incorporated into the economic modelling. The PBAC considered that a model should include post-treatment costs, as in the case of the economic model of brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, recommended at the March and July 2014 PBAC meetings.
- 7.7 The PBAC considered, at the price requested, that the net cost to government may be greater than the estimate in the submission.
- 7.8 The PBAC noted that patients in the PDX-008 trial had a median of 3 lines prior therapy, but considered that a second or later line listing as proposed in the submission was the appropriate clinical place for pralatrexate. The PBAC considered that the following would need to be addressed in a major resubmission: 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 Quality of Life data; and a substantially updated economic evaluation addressing the concerns of ESC and revised financial estimates. The PBAC recalled that brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma was accepted in the ICER range of \$45,000 to \$75,000/QALY and the Committee considered, given uncertainty of clinical benefit, that an ICER at the lower end of this range would be needed in order for pralatrexate to be acceptably cost-effective.
- 7.9 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

PTCL is a rare group of diseases. Once a patient becomes refractory or relapses from 1st line treatment they rely on combination treatments, whose evidence is with b-cell lymphoma patients, rather than in PTCL. Pralatrexate would provide a valid treatment option for these relapsed/refractory PTCL patients. The Sponsor will continue working with the PBAC in order to ensure that pralatrexate is made available to patients who currently have no targeted treatment for their cancer.