7.21 PRALATREXATE
Solution for infusion, 20 mg in 1 mL
Folotyn®, Mundipharma Pty Ltd

1 Purpose of Application

1.1 The minor re-submission sought a Section 100, Authority Required, listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma (PTCL).

2 Requested listing

2.1 The re-submission requested the same listing as in the November 2015 submission except that the effective DPMA has been reduced. The listing below includes the Secretariat's proposed changes as specified in the November 2015 PBAC Public Summary Document (PSD) (paragraph 2).

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

Category / Program	Chemotherapy (Private and Public)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	
Severity:	Relapsed or chemotherapy refractory
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	Relapsed or chemotherapy refractory peripheral T-cell Lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	
Clinical criteria:	Patient must have undergone appropriate prior front-line curative intent chemotherapy
Population criteria:	

Prescriber Instructions	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed PTCL 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.
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). 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 HOBART TAS 7001 **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.

Name, Restriction, Manner of administration and form	Max. Amt	No. of repeats	Published DPMA	Effective DPMA	Proprietary Name and Manufacturer
PRALATREXATE 20 mg in 1 mL, solution for infusion	80 mg	11	$[redacted] (public) $[redacted] (private)	$[redacted] (public) $[redacted] (private)	Folotyn® Mundipharma

Category / Program	Chemotherapy (Private and Public)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	
Severity:	Relapsed or chemotherapy refractory
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	Relapsed or chemotherapy refractory peripheral T-cell Lymphoma
Treatment phase:	Continuing treatment

Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	
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** 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.

2.2 The PBAC noted that patients in the PDX-008 study 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 (paragraph 7.8, pralatrexate Public Summary Document (PSD) November 2015, Item 5.13).

2.3 The minor re-submission states (Section 3.4, page 9) that the Sponsor would be willing to restrict the listing to patients with an ECOG performance status of ≤ 2 for consistency with the majority of patients included in the PDX-008 study and the matched historical cohort.

3 Background

3.1 Pralatrexate was approved by the TGA in January 2015 for adult patients with PTCL who have progressed after at least one prior therapy. The ARTG entry date is 11 August 2015.

3.2 A major submission for pralatrexate for PTCL was rejected at the November 2015 PBAC meeting on the basis of 'insufficient evidence of the incremental clinical benefit against currently available treatments, concerns regarding a high burden of adverse events, and that the economic modelling was not reliable to enable the Committee to determine the cost-effectiveness of the pralatrexate in the Australian context' (paragraph 7.1 pralatrexate PSD November 2015, Item 5.13).

3.3 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' (paragraph 7.8, pralatrexate PSD November 2015, Item 5.13).

3.4 The following table provides a summary of the key differences between the November 2015 submission and this current minor re-submission, including PBAC comments on the November 2015 submission.

Table 1: Summary of the previous submission and current re-submission

	November 2015 submission	March 2016 re-submission
Requested PBS listing	Relapsed or chemotherapy refractory PTCL. **PBAC Comment:** The PBAC considered that a second or later line listing was the appropriate clinical place for pralatrexate (PSD, paragraph 7.8).	No change.
Requested price	$[redacted] ex-man per 20 mg vial. The submission requested a Special Pricing Arrangement with a published price of $[redacted] ex-man per 20 mg vial.	$[redacted] ex-man per 20 mg vial. The same Special Pricing Arrangement is requested (re-submission p3).
Main comparator	A basket of treatments. **PBAC Comment:** The PBAC accepted that the basket of treatments was the appropriate main comparator (PSD, paragraph 7.2).	No change.
Clinical evidence	A matched controlled analysis comparing a subset of patients from PDX-008 who were matched to the historical control cohort. **PBAC comment:** 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 considered the matched cohort analysis was appropriate, however had concerns about the methodology used, where the most optimistic clinical benefit of a small sub-group of patients in the PDX-008 trial were compared to the historical control cohort (paragraph 7.3). The PBAC considered that a major re-submission should present more robust evidence of comparative efficacy and safety (PSD, paragraph 7.8).	No change. The re-submission states (p5) there are no additional pralatrexate clinical studies planned for relapsed or refractory PTCL.
Key effectiveness data	• Median PFS in PDX-008 for pralatrexate was 3.5 months. • Incremental overall survival gain of 13.2 months for pralatrexate compared to historical controls (19 vs 5.8 months), hazard ratio 0.394 (95%CI 0.259 to 0.600). **PBAC Comment:** The PBAC considered there was insufficient evidence of incremental benefit of pralatrexate versus comparators, based on the evidence from PDX-008, in which median PFS 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 (PSD, paragraph 7.4).	.No change. The re-submission considers overall response rate does not predict the durability of response or overall survival in PTCL. The hazard ratio used in the economic model in the November 2015 submission was 0.394. The hazard ratio used in the model for the re-submission is [redacted].
Key safety data	The submission did not present a comparative safety analysis of pralatrexate and comparator treatments. **PBAC Comment:** The PBAC noted in study PDX-008 pralatrexate was associated with high burden of adverse events. The PBAC considered that the evidence presented in the submission did not support the claim of claim of non-inferior comparative safety in the submission (PSD, paragraph 7.5).	No change. The submission re-iterates the toxicity profile of pralatrexate is similar to other chemotherapeutic agents.

	November 2015 submission	March 2016 re-submission
Clinical claim	• Superior in terms of comparative effectiveness over single-agent and combination therapies. • In terms of comparative safety, non-inferior to single-agent therapies and superior to combination regimens. **PBAC Comment:** 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 in the submission was neither informative nor meaningful (PSD, paragraph 7.6).	The pre-PBAC response clarified that no change to the original clinical claim is made in the resubmission.
Economic evaluation	Cost-utility model: • Base case: $45,000/QALY – $75,000/QALY gained (as corrected in PSCR) **PBAC Comment:** The PBAC noted that the ESC considered that the model was not sufficiently reliable to provide a plausible estimate of value for money for the listing of pralatrexate (PSD, paragraph 7.6). The PBAC considered that a major resubmission should present a substantially updated economic evaluation addressing the concerns of ESC (PSD, paragraph 7.8).	Cost-utility model: • Base case: $45,000/QALY - $75,000/QALY gained The following model parameters were changed: • the pralatrexate price was reduced by [redacted]%; • the number of pralatrexate vials was increased by [redacted]% from [redacted] to [redacted] to allow for wastage; • the cost of the comparator was increased from $[redacted] to $[redacted]; and • the HR for overall survival was increased from 0.394 to [redacted]. The model issues noted by the ESC are presented in Table 4 below.
Estimated cost to PBS	$10-$20 million in Year 1 increasing to $20-$30 million in Year 5. **PBAC Comment:** The net cost to government may be greater than the estimate in the submission (PSD, paragraph 7.7). The PBAC considered that revised financial estimates should be provided in a major re-submission (PSD, paragraph 7.8).	Revised financial forecasts not provided. The re-submission states (p15) that the financial impact of the revised pricing proposal can be derived from the previous submission's Section E workbook.
PBAC decision	Reject.	

4 Clinical place for the proposed therapy

4.1 PTCL comprises a group of heterogeneous non-Hodgkin lymphomas that develop from T-cells in different stages of maturity.

4.2 It is proposed that pralatrexate will be administered in the second line for treatment of PTCL.

5 Comparator

5.1 The major submission considered by the PBAC in November 2015 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 PBAC accepted that the basket

of treatments was the appropriate main comparator. This is unchanged in the minor submission.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

6.3 No new clinical data were presented in the minor re-submission. The November 2015 submission included a naïve comparison of:

- PDX-008, a Phase 2, single-arm, open-label, multicentre study conducted in the US, Canada and Europe (N=115).
- A historical control cohort, which consisted of [redacted].
- Matched controlled analysis (MCA) comparing a subset of patients from PDX-008 (n=66), who were matched on a 1:1 basis to the historical control cohort (n=66).

6.4 It is noted in the PSD for the November 2015 submission that the recruitment periods for the historical controls (1984-2011) were older than that of PDX-008 (2006-2008), and that 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 (paragraph 6.11 pralatrexate PSD, November 2015). The minor submission argues that there was significant overlap in the recruitment periods, and it was necessary to utilise multiple databases over long time periods to recruit sufficient patients. Regarding stem cell therapy, the re-submission states data demonstrating a clear benefit on overall survival has not been demonstrated, and this treatment has been used in PTCL since the late 1980s. The re-submission states (p5) the transplantation rate in the matched cohort is unknown.

6.5 It is noted in the PSD for the November 2015 submission that patients in PDX-008 were not matched to historical controls on the basis of ECOG status, and 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 (paragraph 6.11, pralatrexate PSD, November 2015). It was further noted as performance status is a predictive factor of improved outcomes this has the potential to bias the comparison in favour of pralatrexate. The re-submission states (p9) that ECOG was not included as part of the matched analysis, and the sponsor does not have access to further data. The re-submission notes (p9) ECOG data have been reported for 2 of the 4 databases used in the control cohort and 90-98% of patients had an ECOG of 0-2.

6.6 The re-submission states there are no further studies planned assessing the efficacy and safety of pralatrexate in PTCL.

Comparative effectiveness

6.7 The overall survival results for the matched controlled analysis (re-presented in the minor re-submission from the November 2015 submission) are presented in Table 2. A detailed description of the matching methodologies was provided in the Commentary for the November 2015 submission.

Table 2: Summary of the efficacy results from the matched controlled analysis

	N	Median OS (95%CI), months	Absolute difference, months	Hazard ratio (95%CI)
PDX-008 original results				
Pralatrexate	109	14.5 (10.6, 22.5)	NA	NA
PDX-008 updated results[a]				
Pralatrexate	109	14.7 (10.6, 19.8)	NA	NA
Matched controlled analysis: used in base case economic evaluation in November 2015 submission				
Pralatrexate	66	19.0 (11.4,NE)	13.2	0.394 (0.259, 0.600)
Controls	66	5.8 (3.5, 8.0)		
Matched controlled analysis Sensitivity 1: Patients were not matched 1:1, multiple non-unique control patients were matched to each PDX-008 patient				
Pralatrexate	75	[redacted]	[redacted]	[redacted]
Controls	92	[redacted]		
Matched controlled analysis Sensitivity 2: Patients were matched 1:1 without medical review (ie the matching was conducted entirely programmatically). Used in base case economic evaluation in the re-submission.				
Pralatrexate	[redacted]	[redacted]	[redacted]	[redacted]
Controls	[redacted]	[redacted]		

Source: Table 3 paragraph 6.12, pralatrexate PSD November 2015; minor re-submission Table 2 (pg 7); text in italics were compiled during preparation of the overview.

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

[a] Updated results based on additional survival data obtained from 17 patients in the overall trial population. Additional survival data was up to a four year follow-up period

6.8 The PBAC was concerned about the methodology used for the matched cohort analysis in the November 2015 submission, where the most optimistic clinical benefit of a small sub-group of patients in the PDX-008 trial was compared to the historical control cohort. The PBAC noted that the hazard ratio for overall survival in the base case matched controls analysis was 0.394 (95%CI: 0.259, 0.600) while using different matching methodologies, hazard ratio was [redacted] (95%CI: [redacted], [redacted]) and [redacted] (95%CI: [redacted], [redacted]) (paragraph 7.3, pralatrexate PSD, November 2015). The re-submission notes (p5) that the 3 matching methodologies resulted in significantly greater overall survival with pralatrexate, with a [redacted]% reduction in the risk of death. It further notes for each method patients were selected for the pralatrexate and control groups using entirely consistent between-group important clinical criteria, reducing the risk of selection bias and producing generally similar median survival of 17-19 months for pralatrexate and 6-7 months in the control group. The median survival in the control group was noted to be similar to that for gemcitabine-containing regimens ([redacted] months), DHAP ([redacted] months) and chemotherapy regimens as used in a historical database ([redacted] months) (re-submission, Table 2, p7).

6.9 The re-submission used the more conservative hazard ratio of [redacted] from sensitivity analysis 2 in the economic model.

6.10 'The PBAC considered that there was insufficient evidence of incremental benefit of pralatrexate versus comparators, based on the evidence from study PDX-008, in which median PFS 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.' (Paragraph 7.4, pralatrexate PSD, November 2015). The re-submission (p5) and pre-PBAC response (p2) reiterates that the response rate for pralatrexate was similar to that for other currently used treatment regimens. However, the re-submission and pre-PBAC response contends that the overall response rate does not predict the durability of response or overall survival in PTCL. The results from 3 studies and a historical case series are presented to support this claim (Table 3). The re-submission considers the extended duration of response and disease control is likely due to use of continuous therapy.

Table 3: Comparison of outcomes in relapsed/refractory PTCL studies

Treatment	Study	N	PTCL sub-type	Median (range) prior therapies	Median PFS, months	Median OS, months	Median duration of response, months	Overall response (derived from)
New agents								
Pralatrexate	PDX-008	108	PTCL-NOS, ALCL, AITL, transformed MF, other	3 (1, 12)	3.5	14.5	10.1	29% / 39% (independent /investigator)
Brentuximab	Horwitz 2014	34	PTCL-NOS, AITL	2 (1, 9)	2.6	NA	7.6	41.2% (investigator)
Romidepsin	Coiffier 2012	130	PTCL-NOS, ALCL, AITL, enteropathy type TCL, other	2 (1, 8)	4	11.3	17	25% (independent)
Belinostat	O'Connor 2015	120	PTCL-NOS, ALCL, AITL, enteropathy type TCL, other	2 (1, 8)	1.6	7.9	13.6	26% / 23% (independent /investigator)
Historical database case series								
Chemotherapy	Mak 2013	89	PTCL-NOS, AITL, ALCL	1	3.7	6.5	NA	55% (unknown)

Source: re-submission Table 3

Abbreviations: AITL - Angioimmunoblastic T-cell lymphoma, ALCL - Anaplastic large-Cell lymphoma , MF - mycosis fungoides, NA - Not applicable, OS - Overall survival, PFS - Progression free survival, PTCL - Peripheral T-Cell lymphoma, PTCL-NOS - peripheral T-Cell lymphoma no otherwise specified, TCL - T-cell lymphoma.

Comparative harms

6.11 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 considered that the evidence presented in the submission did not support the claim of claim of non-inferior comparative safety in the submission (paragraph 7.5 pralatrexate PSD, November 2015).

6.12 The re-submission states the toxicity profile of pralatrexate is similar to other chemotherapeutic agents, with mucosal inflammation, thrombocytopenia and neutropenia the most commonly reported treatment-related AEs. It notes although thrombocytopenia was a relatively common AE, bleeding complications coincident with the low platelet counts were uncommon, generally mild in severity and predominantly presented clinically as epistaxis. Of the 76 patients (68%) that reported mucositis, the majority (47% of the 68%) were grade 1-2, with 18% grade 3 and 4% grade 4. The serious AEs considered to be related to pralatrexate treatment reported for more than 2 patients in PDX-008 included mucosal inflammation (n = 6, 5%), pyrexia (n = 5, 5%), febrile neutropenia (n = 4, 4%), and thrombocytopenia (n = 3, 3%). Pralatrexate-related serious AEs resulted in withdrawal from treatment of 8 (7%) patients. The re-submission concludes the safety profile of pralatrexate demonstrates that it is well tolerated with manageable AEs, suggesting that the benefit to risk ratio of pralatrexate treatment in this population of patients with relapsed or refractory PTCL is favourable.

Clinical claim

6.13 The re-submission did not explicitly state a clinical claim. The clinical claim in the November 2015 submission was superior efficacy and non-inferior safety. The PBAC agreed with the ESC that there was insufficient clinical evidence to support the claim of superior efficacy and non-inferior safety (paragraph 7.6, pralatrexate PSD November 2015). In the pre-PBAC response of this resubmission, the sponsor provided data that did suggest that the toxicity of pralatrexate was consistent with that observed with other anti-cancer therapies. However, the PBAC considered that these naïve indirect comparisons did not adequately support the claim of superior safety in comparison with combination regimens such as DHAP.

Economic analysis

6.14 The PBAC noted the ESC considered that the model was not sufficiently reliable to provide a plausible estimate of value for money for the listing of pralatrexate (paragraph 7.6, pralatrexate PSD, November 2015). 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. The technical issues with the model noted by the ESC are summarised in Table 4. This table also includes how the re-submission addresses each issue.

Table 4: Summary of the technical issues noted by the ESC for the November 2015 economic model and how addressed in the re-submission

	ESC comments (paragraph 6.24, pralatrexate PSD November 2015)	March 2016 minor re-submission
Costs up front	All costs seem to be included as one off costs up front rather than accruing over time with treatment. The ESC considered this led 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 change to model. The re-submission states (Table 4 p10) the mean duration of pralatrexate treatment is around 16 weeks (maximum of 68 weeks), and very few patients would be treated beyond one year. Therefore the time-value discounting is of no practical relevance to costs.
Health states	No variation of proportion of patients in each response state across treatment arms or with cycle. This resulted in the QALYs being driven by survival, rather than any changes in response to treatment.	No change to model. The re-submission states (Table 4 p11) that there are no data available on the proportion of patients in each response state for the control cohort, and therefore, the Sponsor has to assume that the proportion of patients in each health state will be the same.
Post-progression costs and cost of SCT	No inclusion of post-progression treatment costs and consequences, including stem cell transplant. The PBAC considered the model should include post-treatment costs (paragraph 7.6, pralatrexate PSD, November 2015).	The re-submission considers inclusion of post-progression costs would require an entirely new economic model, and notes that this could not be accommodated within a minor submission (Table 4 p11). The re-submission presents (p14) a sensitivity analysis incorporating post-progression stem cell therapy costs.
Kaplan-Meier	An error impacting survival was corrected in the PSCR and revised ICERs provided. The corrected model indicated that in the pralatrexate arm [redacted]% of patients are still alive and in the comparator arm [redacted]% of patients are still alive at the end of the model. After 5 years, [redacted]% of patients in the pralatrexate arm are still alive and [redacted]% of patients in the comparator arm are still alive. The ESC considered that incremental survival was still overestimated in the model.	The re-submission states (Table 4 p10) the difference is considered to be immaterial to the modelling in the current context and given any adjustment to this would require a major re-submission no further model alteration were undertaken. After 5 years, [redacted]% of patients in the pralatrexate arm and [redacted]% of patients in the control arm are alive. At the end of the model, [redacted]% of patients in the pralatrexate arm and [redacted]% of patients in the control arm are alive.

6.15 In the re-submission (p9) the following model inputs have been revised:

- the pralatrexate price was reduced by [redacted]% (this reduces the ICER);
- the number of pralatrexate vials was increased by [redacted]% from [redacted] to [redacted] to allow for wastage (this increases the ICER);
- the cost of the comparator was increased from $[redacted] to $[redacted] (this reduces the ICER); and
- the HR for overall survival was increased from 0.394 to [redacted] (this increases the ICER).

6.16 The ex-manufacturer cost of a 20 mg vial of pralatrexate was reduced by [redacted]% from $[redacted] to $[redacted]. The dispensed price used in the economic model is $[redacted]. This should be $[redacted] assuming, as in the November 2015 submission, 80% use in public hospitals and 20% use in private hospital (($[redacted][1] x 0.8 + $[redacted] x 0.2)/4). As

1 Includes additional $20 paid to TGA licensed compounders.

the difference is minimal, this would likely have minimal impact on the economic analysis.

6.17 The November 2015 submission estimated that the total number of vials administered to a patient was [redacted]. This was based on the whole population being female and was corrected to [redacted] vials during the evaluation to account for 62% of patients being male with a higher average BSA. During the evaluation it was estimated that 42 vials per patient would be required if wastage was included. The re-submission states (Table 4 p10) 'the evaluation considered that the model did not provide adequately for wastage of vials given that dosing is based on body surface area (BSA). The evaluation had estimated that [redacted] vials would be required (instead of the previous submission's [redacted] vials)'. The [redacted] vials does not include wastage rather it accounts for use in males. Revised ICERs are provided in Table 5 assuming a total of [redacted] vials per patient.

6.18 The cost of the comparator (the basket of treatments) in the November 2015 submission was based on the chemotherapy treatments in the matched historical control cohort (less than $15,000). Regarding this 'the ESC noted that the PSCR (p2) highlighted the conservative nature of the cost of chemotherapy per patient used in the model. It was less than $15,000 (based on the eviQ costings of the matched cohort therapies) whereas the Survey derived current cost of current therapies was $15,000 - $45,000.' The re-submission has utilised the Survey derived cost of therapy ($15,000 - $45,000). Based on the model provided the standard deviation for the cost was also changed from less than $15,000to less than $15,000. Sensitivity analyses using both comparator costs are presented in Table 5.

6.19 The hazard ratio for OS used in the economic model for the November 2015 submission was 0.394. The hazard ratio used in the re-submission is [redacted] based on sensitivity analysis 2. Based on the model provided the overall survival curve for the matched cohort is also revised presumably to reflect the survival curve of the new matched group. These estimates could not be verified, and it could not be verified if the most appropriate parametric function was use.

Table 5: Results of the revised economic evaluation and sensitivity analyses assessing the impact of changing each parameter separately

Scenario	Costs		QALYs		ICER ($/QALY)
	Pralatrexate	Comparator	Pralatrexate	Comparator	
November 2015 major submission [As corrected in the PSCR]	$[redacted]	$[redacted]	2.144	0.784	$[redacted]
Minor re-submission					
Change to base case: • [redacted]% price reduction for pralatrexate ($[redacted] → $[redacted]) • 7% wastage ([redacted] → [redacted] vials per patient) • Comparator cost ($[redacted] → $[redacted]) • HR for overall survival (0.394 → [redacted])	$[redacted]	$[redacted]	1.745	0.784	$[redacted]
Sensitivity analyses: impact of changing each parameter separately (The roll back function in TreeAge was used rather than running a Monte-Carlo simulation to ensure the same results with each sensitivity analysis. Thus the costs and QALYs in the sensitivity analyses use the mean values and differ slightly to those above which used a Monte-Carlo simulation.)					
Change from November 2015: • [redacted]% price reduction for pralatrexate ($[redacted] → $[redacted])	$[redacted]	$[redacted]	2.140	0.786	$[redacted]
Change from November 2015: • [redacted]% wastage ([redacted] → [redacted] vials per patient)	$[redacted]	$[redacted]	2.140	0.786	$[redacted]
Change from November 2015: • [redacted]% wastage ([redacted] → [redacted] vials per patient, as per November 2015 5.13.COM.71)	$[redacted]	$[redacted]	2.140	0.786	$[redacted]
Change from November 2015: • Comparator cost ($[redacted] → $[redacted])	$[redacted]	$[redacted]	2.140	0.786	$[redacted]
Change from November 2015: • HR for OS (0.394 → [redacted])	$[redacted]	$[redacted]	1.740	0.786	$[redacted]
As for minor re-submission with wastage corrected: • [redacted]% price reduction for pralatrexate ($[redacted]) • [redacted]% wastage ([redacted] vials) • Comparator cost $[redacted] • HR for OS [redacted]	$[redacted]	$[redacted]	1.740	0.786	$[redacted]
As for minor submission with wastage corrected and comparator cost as November submission: • [redacted]% price reduction for pralatrexate ($[redacted]) • [redacted]% wastage ([redacted] vials) • Comparator cost $[redacted] • HR for OS [redacted]	$[redacted]	$[redacted]	1.740	0.786	$[redacted]

Source: paragraph 6.26, pralatrexate PSD November 2015,; re-submission p12 and p14; text in italics were compiled during preparation of the overview.

6.20 The re-submission states (p12) that autologous stem cell transplant (SCT), or less commonly, an allogenic SCT, is a common treatment goal for patients with relapsed/refractory T-cell lymphomas. It further states a durable response is more often achieved with single agent therapies such as pralatrexate, allowing patients to proceed to SCT. The re-submission presents (p13-14) the results for two non-randomised studies in which the survival for patients treated with a SCT was longer than for patients not treated with a SCT. In the PDX-008 study, [redacted] ([redacted]%) patients treated with pralatrexate went onto receive a SCT ([redacted] autologous SCT and [redacted]

allogenic SCT) (re-submission, p13). It is unknown what proportion of patient in the matched cohort went onto receive a SCT.

6.21 The re-submission (p14) presents an adjustment to the ICER which includes the cost of a SCT. It is assumed [redacted]% of patients treated with pralatrexate undergo a SCT and the associated cost is $[redacted] ($[redacted] x [redacted]). It is assumed that the transplantation rate for the comparator arm is half that for the pralatrexate arm and the associated cost is $[redacted] ($[redacted] x [redacted]). The cost/QALY gained increases from $45,000 - $75,000 to $45,000 - $75,000. The impact of SCT on the survival outcomes is not discussed in the re-submission. The survival outcomes from PDX-008 include the impact of SCTs. It is unknown if the survival outcomes from the matched cohort include the impact of SCTs.

Drug cost/patient: $[redacted] (ex-manufacturer).

6.22 The total cost of treatment per patient in the November 2015 submission was $[redacted] ($[redacted] x [redacted]). The re-submission states (p15) the estimated cost of pralatrexate for an average patient using [redacted] vials has been reduced to $[redacted] ($[redacted] x [redacted]). The cost of pralatrexate for an average patient using [redacted] vials is $[redacted] ($[redacted] x [redacted]).

Estimated PBS usage & financial implications

6.23 Financial forecasts are not presented in the re-submission, rather it states (p15) that the financial impact of the revised pricing proposal can be derived from the previous submission's Section E workbook.

6.24 A summary of the financial implications using the Section E workbook from the November 2015 submission is presented in Table 6. Using the re-submission's assumption of [redacted] vials per patient, the estimated cost of pralatrexate to the PBS is $10-$20 million in Year 5. Assuming [redacted] vials per patient increases the total net cost to the PBS to $20-$30 million in Year 5. In calculating these estimates the only parameters changed are the cost per vial and number of vials per patient. Additional concerns regarding the financial forecasts presented in the November 2015 submission are noted in paragraph 6.34 of the November 2015 PSD.

Table 6: 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)	%	%	%	%	%
Market share (all other patients)	%	%	%	%	%
Scripts*					
November 2015 Estimated net cost to PBS/RPBS					
DPMA $ per vial, 32.9 vials per patient	$	$	$	$	$
Minor re-submission estimated net cost to PBS/RPBS					
DPMA $ per vial, 35.2 vials per patient	$	$	$	$	$
DPMA $ per vial, 42 vials per patient	$	$	$	$	$

Source: Table ES8 of the Commentary of the November 2015 submission, Table E.6.3, pE38 of the submission, Folotyn – Section E Base Case (Ver10).xlsx, sheet Net Cost to PBS

*Assuming 14 scripts per person as estimated by the November 2015 submission

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, as well as concerns regarding the burden of adverse events, and that the economic modelling was insufficiently reliable to enable the Committee to determine the cost-effectiveness of the pralatrexate in the Australian context.

7.2 The PBAC reiterated that there is a clinical need for new effective treatments for the relapsed or refractory peripheral T-Cell lymphoma, but considered that it remained unclear if pralatrexate provided additional health benefits compared to current treatments available to patients.

7.3 The PBAC noted the modifications made to parameters of the economic model, including the cost of pralatrexate and the comparators, allowing for wastage and the hazard ratio for overall survival. The PBAC considered that the resubmission had not addressed the technical concerns that PBAC had with the economic model nor the fundamental issue of the meaningfulness of this type of economic evaluation when there was insufficient clinical evidence to support the claim of superior efficacy and superior safety over combination chemotherapy regimens.

7.4 The PBAC remained of the view 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.

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

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The Sponsor will continue working with the PBAC in order to ensure that pralatrexate is made available to PTCL patients who currently have no targeted treatment for their cancer.