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

1 Purpose of Application

1.1 The minor resubmission requested an Authority Required listing for the treatment of peripheral T-cell lymphoma (PTCL). This minor resubmission sought to address the economic issues noted in the July 2017 Public Summary Document (PSD).

1.2 In July 2017, the PBAC requested more conservative assumptions in the economic model in any future resubmission, that includes:

- a lower stem cell transplant (SCT) rate in the comparator arm than the pralatrexate arm, noting that Australian data indicated that this was approximately 27%
- at least two lines of subsequent therapy
- the removal of brentuximab from the cost-offsets
- a substantial price reduction, to account for the associated uncertainty in the incremental clinical benefit (noting overall survival for pralatrexate patients was overestimated (18.8 months) in the economic model, when compared to results from PDX-008 (14.7 months) (July 2017 PSD; para 7.8 and 7.11).

1.3 The following issues were addressed in this minor resubmission:

- Brentuximab has been removed from comparator costs in the economic model
- A [redacted]% price reduction from the July 2017 price was offered, with the ex-manufacturer price reduced to $[redacted] per 20 mg/mL vial.

1.4 Sensitivity analyses were provided in the resubmission to address the rates of SCT and allowing for two subsequent lines of therapy.

2 Requested listing

2.1 There was no change to the requested listing in this minor resubmission from the proposed listing in July 2017. The PBAC reaffirmed in July 2017 that a second or later line listing as proposed was the appropriate clinical place for pralatrexate (July 2017 PSD; para 7.3).

2.2 In July 2017, the PBAC considered a phone authority would be appropriate for both initiating and continuing patients, as there was low risk of use outside the requested use in PTCL (July 2017 PSD; para 2.5).

2.3 The essential elements of the listing are as follows:

Name, Restriction, Manner of administration and form	Max. Amt	№.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.

3 Background

3.1 Pralatrexate was registered by the Therapeutic Goods Administration (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 three previous occasions. The first major submission was considered in November 2015, a minor resubmission was considered in March 2016 and a second major resubmission was considered in July 2017.

4 Comparator

4.1 No change was made to the basket of comparators from the July 2017 resubmission, although the brentuximab costs were removed from the comparator arm in the economic model.

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (1) via the Consumer Comments facility on the PBS website. The comment highlighted the tolerability and effectiveness of pralatrexate in a patient with PTCL.

Comparative effectiveness

5.3 No new evidence was presented compared with the July 2017 resubmission. For the determination of overall survival 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 = 386). These data were included in the previous submissions; and
    - One Australian database: Peter MacCallum Institute (N = 83). These data were new to this resubmission.

5.4 The previous claim was that pralatrexate was superior in effectiveness and had comparable or non-inferior safety compared to the basket of comparator treatments.

5.5 In paragraphs 7.5, 7.6 and 7.7 of the July 2017 PSD for pralatrexate, the Committee maintained that the clinical evidence presented was insufficient for establishing a meaningful overall survival benefit, as:

- key confounders, particularly prognostic factors such as lactate dehydrogenase (LDH), extranodal disease, stage, presence or absence of B symptoms, were imbalanced across the three patient cohorts;
- OS in the combined historical control cohort (5.0 months (95% CI: 4.1, 6.7)) 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.

5.6 In July 2017, (PSD paragraph 7.6) the PBAC considered the fundamental flaw in the data presented was that the submission compared outcomes of patients prospectively accrued into a clinical trial with 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 could not be overcome fully, neither by the approaches taken in the July 2017 resubmission, nor the matched analysis used previously in November 2015. In July 2017, the PBAC therefore considered that the survival benefit had 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.

5.7 In July 2017, (PSD paragraph 7.7) 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.

Economic analysis

5.8 In the July 2017 resubmission, a stepped cost-utility analysis was presented with an incremental cost-effectiveness ratio (ICER) of $45,000/QALY - $75,000/QALY gained. A summary of the outstanding issues with the economic model from July 2017 and the sponsor's response to the issues in this minor resubmission is shown in Table 1.

5.9 With the reduced price proposed for pralatrexate in this minor resubmission and the removal of brentuximab costs from the comparator arm, the revised base case ICER was $15,000/QALY - $45,000/QALY gained. The ICERs presented in the minor submission were verified by the Secretariat.

Table 1: Summary of economic issues identified in July 2017 consideration of the major submission

Matters of concern (July 2017)	How the resubmission addresses it
OS for pralatrexate patients was overestimated (18.8 months) in the economic model, when compared to results from PDX-008 (14.7 months). (para 7.8; 7.11)	The modelled OS has not been altered. It was argued that PDX-008 patients were on average older, with worse ECOG status, and more prior line of treatment than the control patients. The Cox-Regression adjustment of the OS Kaplan Meier results for population differences was argued to reflect a well-accepted methodology. In July 2017, the PBAC considered a major limitation to 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, was that it could not be applied for the historical control cohort, as no individual patient data were available for comparison with the modelled estimates. (para 6.31)
It was inappropriate to have included brentuximab in the nominated basket of comparators. (para 7.3; 7.11)	Brentuximab has been removed from comparator costs in the economic model and consequently the average number of expected cycles of chemotherapies was also reduced from 5.85, in the July 2017 base case, to 5.31.
The differences in rates of SCT between the two arms could likely reflect the different intents of therapy in this non-randomised comparison, again emphasising the inherent uncertainty in the approach. (para 7.8; 7.11)	The modelled rates of SCT have not been altered in the base case. Adjusting the model for 27% SCT in both arms and amending the survival gain was tested in a sensitivity analysis, increasing the ICER to $15,000/QALY - $45,000/QALY from $15,000/QALY - $45,000/QALY in the revised base case.
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 ($45,000/QALY - $75,000/QALY) for two subsequent line of therapy compared with $45,000/QALY - $75,000/QALY for the base case. (para 7.8; 7.11; Table 13)	The number of subsequent lines of treatment has not been altered in the base case. Sensitivity analysis allowing for two subsequent lines of therapy increased the ICER to $15,000/QALY - $45,000/QALY from $15,000/QALY - $45,000/QALY in the revised base case.
Any future major resubmission should include… a substantial price reduction, to account for the associated uncertainty in the incremental clinical benefit. (para 7.11)	New price offer for pralatrexate is $[redacted] ex-man per 20 mg / mL vial (previously $[redacted]). This represents a [redacted]% price reduction. The requested published price is $[redacted] ex. man. per vial (previously $[redacted]).

Source: Summarised from the November 2017 minor resubmission for pralatrexate
Note: Paragraph and Table references for July 2017 refer to the pralatrexate PSD.

Drug cost/patient/course: $[redacted] (private).

5.10 In the July 2017 resubmission, the total drug cost/patient/course of pralatrexate treatment was calculated to be $[redacted], based on an ex-manufacturer price of

$[redacted]/vial and 40.4 vials per patient, which was derived from individual patient data from study PDX-008. This represented a mean of 14 doses per patient or 2.3 cycles.

5.11 In this minor resubmission, the total drug cost/patient/course of pralatrexate treatment has been reduced to $[redacted] (at DPMA, private hospital), based on the revised ex-manufacturer price of pralatrexate of $[redacted] per 20 mg vial, an average of 3 vials per dose and 14 doses per patient.

Estimated PBS usage & financial implications

5.12 The minor resubmission estimated the revised net cost to the PBS/RPBS of $10 - $20 million in the sixth year of listing, with a total net cost to the PBS/RPBS of $60 - $100 million over the first 6 years of listing. This is summarised in the table below together with the estimated number of patients treated and prescriptions.

Table 2: Revised financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indicative net cost to Medicare Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government for MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall Net Cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] assuming 1 prescription per dose (this equates to 14 scripts per year based on the mean doses from trial PDX-008,)
[b] The reduction in hospital costs is due to the assumed reduction in hospital admissions for the treatment of febrile neutropenia.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

6 PBAC outcome

6.1 The PBAC recommended the S100 Efficient Funding of Chemotherapy Program Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL), on the basis that the substantially reduced price for pralatrexate adequately addressed the uncertainty with the cost-effectiveness estimates, noting that pralatrexate will fulfil a clinical need.

6.2 The PBAC did not consider use of pralatrexate outside the proposed restriction was likely and hence considered that a risk share agreement would not be required.

6.3 The PBAC recommended a telephone rather than a written authority for both initial and continuing applications (as per July 2017 PSD).

6.4 The PBAC did not consider a separate grandfathering restriction was required, based on the wording of the proposed initial restriction.

6.5 The PBAC noted that the Early Supply Rule does not apply to antineoplastic agents.

6.6 The PBAC advised that pralatrexate is not suitable for prescribing by nurse practitioners.

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

6.8 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome

Recommend

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
PRALATREXATE, Solution for I.V. infusion 20 mg in 1 mL	80 mg	5	Folotyn	Mundipharma Pty Ltd.

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	Peripheral T-cell Lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	Patient must have undergone appropriate prior front-line curative intent chemotherapy AND The condition must be relapsed or chemotherapy refractory.
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
PRALATREXATE, Solution for I.V. infusion 20 mg in 1 mL	80 mg	11	Folotyn	Mundipharma Pty Ltd.

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	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
Clinical criteria:	The condition must be relapsed or chemotherapy refractory. AND Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

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 is pleased that pralatrexate has received a positive recommendation from the PBAC and is looking forward to making pralatrexate available to the Australian community.