

5.17 AMINO ACID FORMULA WITHOUT PHENYLALANINE, 110g modified release tablet x 4, bottle, PKU Easy Microtabs®, Orpharma Pty Ltd.

1 Purpose of Application

1.1 The minor submission requested a restricted benefit listing for phenylketonuria (PKU).

2 Requested listing

2.1 The submission’s requested listing is shown below:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
AMINO ACID FORMULA WITHOUT PHENYLALANINE Modified release, 4 x 110 g, bottle	5	5	\$ [REDACTED]	PKU Easy Microtabs®	Orpharma Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input 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
Condition:	Phenylketonuria
PBS Indication:	Phenylketonuria

3 Background

3.1 PKU Easy Microtabs® does not require registration with the TGA. The sponsor confirms that it meets the requirements for foods that have medical purposes as set out under *The Australia New Zealand Food Standards Code — Standard 2.9.5: Food for Special Medical Purposes*.

3.2 PKU Easy Microtabs® has not been considered by the PBAC previously.

4 Comparator

- 4.1 The submission nominates Phlexy-10® standard release tablet as the main comparator. Both PKU Easy Microtabs® and Phlexy-10® are tablets containing essential and non-essential amino acids, without phenylalanine.

5 PBAC 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 that no consumer comments were received for this item.

Consideration of the evidence

- 5.3 A clinical study compared the use of PKU Easy Microtabs® (utilising a different brand available overseas) with conventional amino acid substitutes (i.e. the type used at baseline) in children with PKU (N=55), hyperphenylalaninemia (N=60) and unaffected subjects (N=60) (Giovannini, M., Riva, E., et al. (2014). "Randomized controlled trial of a protein substitute with prolonged release on the protein status of children with phenylketonuria." Journal of the American College of Nutrition 332: 103-110.).

Table 1: Protein status and phenylalanine levels in children receiving slow release or conventional amino acid substitute at baseline and end of trial

Variable	Children with PKU		P value [†]
	Slow-release substitute (N=27)	Conventional substitute (N=28)	
Protein status:			
Albumin (g/dL)			
Baseline	4.5 (0.2)	4.5 (0.2)	0.885
End of study	4.6 (0.2)	4.5 (0.2)	0.334
P value [‡]	0.068	0.537	
Transthyretin (mg/dL)			
Baseline	19.1 (6.4)	19.0 (6.3)	0.986
End of study	20.7 (6.8)	19.2 (6.0)	0.385
Mean change (95% CI)	1.6 (0.4, 2.8)		
P value [‡]	0.017*	0.350	
RBP (mg/L)			
Baseline	25.6 (10.0)	25.6 (9.5)	0.997
End of study	26.1 (10.1)	25.5 (8.7)	0.856
P value [‡]	0.167	0.926	

Variable	Children with PKU		P value ⁺
	Slow-release substitute (N=27)	Conventional substitute (N=28)	
AA ratio			
Baseline	2.6 (0.9)	2.6 (0.8)	0.897
End of study	2.7 (0.8)	2.6 (0.8)	0.588
P value [‡]	0.536	0.945	
Phenylalanine, mean plasma concentration (SD), mg/dL & µmol/L^α:			
Baseline	6.22 (5.4) mg/dL 377 (327) µmol/L	5.96 (5.02) mg/dL 361 (304) µmol/L	0.887
End of study	4.47 (4.08) mg/dL 270 (247) µmol/L	5.56 (4.92) mg/dL 337 (298) µmol/L	0.183
Mean change (95% CI)	-1.75 (-3.34, -0.16) mg/dL -106 (-60, -10) µmol/L	-0.40 (-2.11, 1.31) mg/dL -24 (-128, 79) µmol/L	
P value	NR	NR	

Source: table B.2-1 of the submission, page 21

AA = nonessential to essential amino acids ratio, NR = not reported, PKU = phenylketonuria, RBP = retinol-binding protein. Values are means (SD).

+ Significance of between-group difference (independent samples t-test or Mann-Whitney test).

‡ Significance of within-group difference (paired samples t test or Wilcoxon test).

α Converted from mg/dL using 1mg/dL = 60.54 µmol/L

*Statistically significant. Significance of difference between PKU groups with 2-way analysis of variance was $p > 0.674$ for any variable.

- 5.4 At the end of the study it found statistically significantly greater effect on transthyretin concentrations in PKU patients (refer Table 1). It was suggested that ingestion of the prolonged release substitute contributed to better regulation of protein status, with more harmonised protein synthesis due to longer retention of proteins.
- 5.5 The clinical trial data has demonstrated statistically significant improvements in protein status and plasma phenylalanine concentrations in children with PKU receiving PKU Easy Microtabs® supplements for one month.
- 5.6 The clinical trial results suggest that the slow release amino acid tablet formulation PKU Easy Microtabs® may provide a benefit over other amino acid formulations for some people, demonstrating the importance of slow release formulation as an additional treatment option in phenylketonuria. As a minor submission, the clinical evidence was not evaluated.
- 5.7 PKU Easy Microtabs® are formulated as convenient, easy to swallow tablets whereas Phlexy-10 tablets are much larger, similar to a large vitamin tablet, limiting their use to older children and adults able to swallow larger tablets.
- 5.8 In consideration of the submission, the Nutritional Products Working Party (NPWP) noted:
- The nominated comparator for this product, Phlexy-10®, was appropriate as the products have a similar amino acid composition, but the NPWP considered that other products that included vitamins and minerals could potentially be considered as comparators.

- This product has several benefits, including small size and a lack of taste and odour.
- The authors of the cited clinical trial comment that longer and adequately powered longitudinal studies are required to assess the effective value of protein substitutes with prolonged release, and the NPWP agreed with this comment. Overall, the clinical trial results suggest that the slow release amino acid tablet formulation PKU Easy Microtabs® may provide a benefit over other amino acid formulations for some people.
- The NPWP considered that the listing of this product may not be cost-neutral to the PBS. PKU Easy Microtabs® are not a complete nutritional product and patients may need to supplement their consumption with vitamins and minerals, such as Paediatric Seravit®. If uptake of PKU Easy Microtabs® is greater than substitution of only Phlexy-10®, an additional cost to the PBS and/or the patient may be incurred as patients may need to supplement their diet with additional vitamins and minerals.
- The cost per gram of protein equivalent was used to derive the price of PKU Easy Microtabs® compared to Phlexy-10®. In light of the financial concerns (that is, the additional costs for vitamin and mineral supplementation), it is appropriate to review the pricing arrangements for similar products, such as Phlexy-10®, as this may not have been fully considered previously by the NPWP and PBAC.

5.9 The NPWP supported the listing of PKU Easy Microtabs® as a Restricted Benefit for phenylketonuria on a cost-minimisation basis against Phlexy-10® at an equivalent price per gram of protein.

Estimated PBS usage & financial implications

Table 2: Cost to the PBS of PKU Easy Microtabs® listing over the first 6 years.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total units*	■	■	■	■	■	■
Cost at DPMQ	\$■	\$■	\$■	\$■	\$■	\$■
Cost at DPMQ with average co-payment removed	\$■	\$■	\$■	\$■	\$■	\$■

Source: table E 2-4 of the submission, page 27, based on the DPMQ in the submission. * 1 unit = proposed PBS maximum quantity.

5.10 The submission assumes ■ dispensing per year for this product. The submission expects the listing of PKU Easy Microtabs® to be cost neutral as it is at the same cost per gram of protein equivalent as the comparator, and all usage will substitute for currently listed therapies, there is no expected net cost of PBS listing.

6 PBAC Outcome

6.1 The PBAC recommended the listing of PKU Easy Microtabs® as a Restricted Benefit for the treatment of phenylketonuria on a cost-minimisation basis against Phlexy-10® listing at the same price per gram of protein.

- 6.2 The PBAC noted and agreed with Nutritional Products Working Party’s (NPWP) view that the nominated comparator for this product, Phlexy-10®, was appropriate as the products have similar amino acid composition.
- 6.3 The PBAC noted the NPWP’s comments on the benefits of this product for patients with PKU.
- 6.4 In accordance with subsection 101(3BA) of the Act the PBAC advised that, on the basis of the material available to its November 2015 meeting, PKU Easy Microtabs® should not be treated as interchangeable on an individual patient basis with any other drugs.
- 6.5 The PBAC recommended that PKU Easy Microtabs® is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.
- 6.6 The PBAC recommended that the Safety Net 20 Day Rule should not apply as it has been the PBAC’s view that general nutrients be exempt.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

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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 thanks the PBAC for their considerations.