

**4.01 AMINO ACID FORMULA WITH FAT, CARBOHYDRATE, VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE AND SUPPLEMENTED WITH DOCOSAHEXAENOIC ACID,
Oral liquid, 20 x 500 mL bottles;
PKU Baby®; Orpharma Pty Ltd.**

1 Purpose of Application

1.1 The minor submission requested a Restricted Benefit listing for phenylketonuria.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
AMINO ACID FORMULA WITH VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE Amino acid formula with vitamins, minerals and long chain fatty acids without phenylalanine containing 10 g protein, oral liquid, 500 mL bottle, 20	1	5	\$ [REDACTED]	PKU Baby	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
Condition:	Phenylketonuria
PBS Indication:	Phenylketonuria
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

3 Background

3.1 PKU Baby does not require registration with the TGA. The sponsor confirmed 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 Baby was considered by the Nutritional Products Working Party (NPWP) in September 2015 and the PBAC in November 2015.
- In September 2015, the NPWP deferred its consideration of the submission until such time that clarification from the sponsor could be sought regarding whether the product meets “Australia New Zealand Food Standards Code - Standard 2.9.1 - Infant Formula Products.
 - In November 2015, the PBAC noted that the sponsor provided additional information post-submission to address the NPWP concerns. The PBAC then deferred its recommendation until further advice could be provided by the NPWP on the submission in view of this additional information. At that time, the PBAC also noted “the price proposed in the submission and agreed with the NPWP that no additional health benefit had been demonstrated by this product compared to the currently listed alternatives.”
- 3.3 The NPWP considered the additional information for this submission in January 2016, and its updated advice is noted below under ‘Consideration of the evidence’.

4 Comparator

- 4.1 The submission nominates PKU Anamix Infant as the main comparator. PKU Baby and PKU Anamix Infant both are taken as oral liquids and both products contain 2g of protein equivalent per 100mL of liquid. However, PKU Anamix Infant requires reconstitution prior to use.

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 that no consumer comments were received for this item.

Consideration of the evidence

Table 1: Clinical comparison of PKU Baby and powdered amino acid formulas (Stroem, Enggaard et al. 2011)

Citation	Stroem, P., Enggaard, K., et al. (2011). "When will PKU infants blood phenylalanine reach the desired level? - a study of 207 PKU patients." J Inherit Metab Dis 34(Suppl 3): S101. <i>The sponsor did not provide full details of the clinical study and the attachment 7 is a conference abstract.</i>
Objective	To determine if there is a time difference as to when infants blood phe reached the desired level, depending on which phenylalanine free infant formula was used.
Formulas used	Liquid formula: PKU Baby Powdered formulas: PKU Anamix Infant (Nutricia), XPhe (MetaX), 2 other powder formulas that are no longer marketed in Denmark. (Source: Direct communication with Kennedy Centre authors).
Patients	207 PKU patients treated from birth at the Kennedy Centre, Denmark
Methods	PKU infants were divided into 3 groups according to phenotype – classical, moderate, and mild. Five different formulas – 1 liquid (PKU Baby), 4 powdered – were administered to the 3 patient groups. Number of days from start of treatment to blood phe reaching the desired level below 300 µmol/L (until year 2000 420 µmol/L) was recorded.
Results	Median number of days to reach desired blood phe level: Classical (N=115): Liquid 6 days vs. powdered 8-18 days. Moderate (N=11): Liquid (-) days vs. powdered 5-12 days. Mild (N=80): Liquid 4 days vs. powdered 5-8 days.

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

- 5.3 The clinical trial, reported as a conference abstract, compared the use of PKU Baby and 4 other amino acid powder formulations, including the comparator PKU Anamix Infant. An overview of the clinical study and the results is provided in the table above.
- 5.4 The submission claimed that the study demonstrated that the PKU Baby liquid formula seems to be more efficient than the powdered formulas in reaching the desired blood phenylalanine level (below 300 µmol/L).
- 5.5 The submission states that therapeutic conclusion is that PKU Baby is equivalent or potentially superior to the comparator PKU Anamix Infant. As a minor submission, the clinical evidence was not evaluated.
- 5.6 In September 2015, in consideration of the submission, the NPWP noted:
- The comparator PKU Anamix Infant® is appropriate, and has a similar amino acid composition to PKU Baby®. Although there are some differences to the vitamin and mineral profiles (such as iron), the clinical impact is uncertain.
 - The sponsor requested a price premium per gram of protein. The NPWP noted the reasons for the request for a price premium but considered that there was no additional benefit expected from this product compared to the currently listed alternatives. Although the submission claimed that phenylalanine levels in the study participants normalised swiftly, there was no evidence to suggest that this would significantly alter patient outcomes. The NPWP was concerned that the clinical claim in the submission may not be supported by the evidence provided.

The non-peer-reviewed abstract contained no information about the initial phenylalanine levels of participants, the number of patients on liquid versus powder, no randomisation of participants, and no presentation of standard errors. Overall, the NPWP viewed that in practice this product would likely provide the same health benefit to patients as the alternatives listed on the PBS.

- The sponsor claimed that this liquid product would result in less wastage than a powder product. The NPWP disagreed with this claim, noting that in clinical practice, patients are usually advised to use all prescribed product before switching products, or any excess cans for powders are used by other patients in the clinic.
- Following the above considerations, listing this product on the equivalent price per gram of protein as per the comparator, PKU Anamix Infant® was appropriate.
- The sponsor underestimated the quantity of this product required by an infant. Specifically, the sponsor estimated that 6 months' supply would provide 280mL/day (500mL x 20 x 5/180 days). However, infants are more likely to require 400-500mL (280-350 calories) per day, even considering supplemental breast/formula feeds and solids. Therefore, the NPWP considered the number of bottles (20) to be insufficient for a month's supply, as recommended in the PBAC Guidelines.
- Although the sponsor stated that this product meets "Australia New Zealand Food Standards Code - Standard 2.9.5 - Food for Special Medical Purposes", the NPWP noted that the submission, for a formula proposed to be used in infants younger than 12 months, did not provide a comparison with the requirements of the "Australia New Zealand Food Standards Code - Standard 2.9.1 - Infant Formula Products", as recommended in the PBAC Guidelines.

5.7 In January 2016, in consideration of information received post-submission, the NPWP noted that:

- The sponsor provided a suitable comparison against the requirements of the "Australia New Zealand Food Standards Code - Standard 2.9.1 - Infant Formula Products".
- The sponsor provided further reasoning, and additional clinical data, to support its claim for a price premium per gram of protein over the comparator product. Nonetheless, the NPWP reconfirmed its advice that the level of evidence provided did not justify the claim that this product provided improved clinical outcomes when compared to the currently listed alternatives.
- In terms of the maximum quantity, the sponsor noted the NPWP's advice that the requested quantities may be insufficient for a months' supply, as recommended in the PBAC Guidelines. The sponsor suggested that feedback from overseas markets indicated that the proposed 20 bottles would be sufficient, but was nonetheless agreeable to amending the maximum quantities.

5.8 The NPWP supported the listing of PKU Baby® as a Restricted Benefit for phenylketonuria on a cost-minimisation basis against PKU Anamix Infant® at an equivalent price per gram of protein. The NPWP advised that PKU Baby® should be listed with a maximum quantity that is comparable to currently listed comparators.

Estimated PBS usage & financial implications

Table 2: Cost to the PBS of PKU Baby 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 without average co-payment	\$■	\$■	\$■	\$■	\$■	\$■

Source: Table E.2-4 of the submission, page 26

* 1 unit = proposed PBS maximum quantity.

- 5.9 The submission requested a higher price per gram of protein compared with the comparator because of the higher cost of goods of PKU Baby, clinical importance of an alternative PKU product for infants and the potential clinical advantages shown by PKU Baby in the clinical study. The DPMQ requested in the submission represented an AEMP of \$■ per gram of protein content. The AEMP for PKU Anamix Infant is \$1.49 per gram of protein.
- 5.10 The submission assumed that less than 10,000 units of PKU Baby would be dispensed in year 1, increasing to less than 10,000 in year 6. Though the product is expected to replace other PBS listed products for PKU, at the price requested, there is an additional cost to the PBS estimated to be less than \$10 million in year 1 and less than \$10 million in year 5.

6 PBAC Outcome

- 6.1 The PBAC recommended listing amino acid formula with fat, carbohydrate, vitamins, minerals and long chain fatty acids without phenylalanine and supplemented with docosahexaenoic acid Oral liquid 500 mL, 20 (PKU Baby) as a Restricted Benefit for phenylketonuria on a cost-minimisation basis against amino acid formula with vitamins, minerals and long chain polyunsaturated fatty acids without phenylalanine, Oral powder 400 g (PKU Anamix Infant) at an equivalent price per gram of protein.
- 6.2 The PBAC noted the advice of the NPWP that supported the listing of PKU Baby® on the PBS, following its consideration of additional information received from the sponsor post-submission.
- 6.3 The PBAC noted additional clinical data provided post-submission to support this claim of a price premium over the comparator product, but agreed with the NPWP that the level of evidence provided did not justify the claim that this product provided improved clinical outcomes when compared to the currently listed alternatives.
- 6.4 The PBAC recommended that PKU Baby® should be listed with a maximum quantity that is comparable to currently listed comparators. In this regard, PKU Anamix Infant® is listed with a maximum quantity of 8 cans and 5 repeats. Noting that PKU Baby is manufactured in packs of 20 bottles, the PBAC therefore considered that a maximum quantity of 2 packs of 20 bottles, with 5 repeats would be suitable on the basis of per gram of protein.

- 6.5 In accordance with subsection 101(3BA) of the Act, the PBAC advised it is of the opinion that, on the basis of the material available to it at its March 2016 meeting, PKU Baby® should not be treated as interchangeable on an individual patient basis with any other drugs.
- 6.6 The PBAC recommended that PKU Baby® is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.
- 6.7 The PBAC recommended that the Early Supply 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:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
AMINO ACID FORMULA WITH FAT, CARBOHYDRATE, VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE AND SUPPLEMENTED WITH DOCOSAHEXAENOIC ACID Amino acid formula with fat, carbohydrate, vitamins, minerals and long chain fatty acids without phenylalanine and supplemented with docosahexaenoic acid oral liquid, 20 x 500 mL bottles	2	5	PKU Baby	Orphama Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
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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 had no comment.