

5.17 AMINO ACID FORMULA WITH VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS, WITHOUT PHENYLALANINE

Oral powder 400 g (PKU Start),
PKU Start[®],
Vitaflo Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested a Restricted Benefit listing for a new form of amino acid formula with vitamins, minerals and long chain polyunsaturated fatty acids without phenylalanine for the dietary management of phenylketonuria (PKU).

2 Requested Listing

- 2.1 The submission requested the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
AMINO ACID FORMULA WITH VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE powder for oral liquid, 400 g	8	5	\$722.75*	PKU Start Vitaflo Pty Ltd Australia

*calculated by the Department

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

3 Background

- 3.1 The sponsor of PKU Start 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 The sponsor also confirmed that it complies with *Standard 2.9.1: Infant Formula Products for specific dietary use*.

- 3.3 The submission noted that PKU Start contains choline (7.3 mg/100kj) that is 2.8% higher than the maximum permitted amount for the Standard 2.9.1. The submission claimed that the slightly higher amount of choline is not detrimental to infants.
- 3.4 The submission noted that PKU Start provides 70% of iron requirements for infants aged 7-12 months. The submission claimed that infants in this age group would usually be taking a second stage protein substitute. The submission claimed that PKU Start in combination with a second stage protein substitute would be sufficient to meet iron requirements in this age group.
- 3.5 PKU Start has not been previously considered by the PBAC.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor submission nominated PKU Anamix Infant as the comparator, as it is an oral powdered protein substitute for infants with PKU. The Sponsor requested to list PKU Start on a cost-minimisation basis per gram of protein of PKU Anamix Infant.
- 4.2 The sponsor claimed that while PKU Baby (PBS Code 10822N) is another similar product, it is presented in liquid form and therefore not a true comparator.
- 4.3 PKU Baby was listed as a Restricted Benefit for PKU on cost-minimisation basis against PKU Anamix Infant at an equivalent price per gram of protein at the March 2016 PBAC meeting.
- 4.4 PKU Start contains 57.2 g protein per 400 g, which is higher than PKU Anamix Infant (52.4 g protein per 400 g).
- 4.5 PKU Start contains 40% more docosahexaenoic acid (DHA, 0.014 g/100 mL) than the nominated comparator, PKU Anamix (0.01 /100 mL). It also has higher content of most water-soluble vitamins; including folic acid than the comparator.
- 4.6 Iron, manganese and chromium in PKU Start are also higher than nutrient reference values (NRVs) for the 0 to 6 months age group.

For more detail on PBAC's view, see section 6 PBAC outcome.

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.

Clinical trials

- 5.3 As a minor submission, no clinical trials were presented in the submission.
- 5.4 In consideration of the submission, the Nutritional Products Working Party (NPWP) noted that:
- The sponsor provided a suitable comparison against the requirements of *The Australia New Zealand Food Standards Code – Standard 2.9.5: Food for Special Medical Purposes*.
 - PKU Start® provides 70% of iron requirements for infants aged 7-12 months. The submission claimed that infants in this age group would usually be taking a second stage protein substitute and that PKU Start in combination with a second stage protein substitute would be sufficient to meet iron requirements in this age group. However, the NPWP noted that a second stage protein supplement in infants with PKU is generally started later in Australia and that considered that the reduced iron content in PKU Start® may cause iron deficiency in this age group.
- 5.5 The PBAC noted that the NPWP did not support the proposed listing. The NPWP considered that the sponsor should provide a clinical justification for the low iron level in PKU Start®, before any possible recommendation to list could be made to PBAC.

Estimated PBS usage & financial implications

- 5.6 The submission proposed that PKU Start be cost-minimised to PKU Anamix Infant at an equivalent price per gram of protein equivalent (PE) as PKU Anamix Infant. The minor submission calculated the AEMP per can to be \$80.65 based on the cost of \$1.41 per gram of PE.
- 5.7 The submission claimed that the listing of PKU Start is expected to be cost neutral to the PBS as it would only replace the utilisation of its comparator, PKU Anamix Infant. However, the Department noted that the listing of PKU Start would result in a small cost to the PBS from direct substitution, due to the higher protein content compared with PKU Anamix Infant.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC decided to defer its decision on whether to recommend the listing of amino acid formula with vitamins, minerals and long chain polysaturated fatty acids, without phenylalanine for the dietary management of PKU. The PBAC considered there was a lack of clinical justification for the low iron level of the product in the submission but noted that the sponsor provided a pre-PBAC response attempting to

address this issue and considered that the response should be considered by the Nutritional Products Working Party (NPWP) before finalising its decision.

- 6.2 The PBAC noted that the product provides only 70% of iron requirements for infants aged 7-12 months.
- 6.3 The PBAC noted that the NPWP supported the decision of deferral on the listing of the product on the PBS to allow the sponsor to provide further clinical justification on the product's iron content.
- 6.4 The PBAC noted the pre-PBAC response from the sponsor and considered that input from the NPWP was required to assess whether the response adequately justified their claims.
- 6.5 The PBAC noted that this submission is not eligible for an Independent Review as it has been deferred for further discussion.

Outcome:

Deferred

7 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.

8 Sponsor's Comment

The sponsor had no comment.

Addendum to the November 2017 PBAC Minutes:

**4.01 AMINO ACID FORMULA WITH VITAMINS, MINERALS
AND LONG CHAIN POLYUNSATURATED FATTY ACIDS,
WITHOUT PHENYLALANINE
Oral powder 400 g (PKU Start),
PKU Start[®], Vitaflo Australia Pty Ltd**

1 Background

At the November 2017 PBAC meeting, the PBAC noted the NPWP advice and considered that there was a lack of clinical justification for the low iron level in PKU Start. However, the committee noted the pre-PBAC response from the sponsor and decided to defer their decision on PKU Start to allow for consideration of the pre-PBAC response by the NPWP.

Sponsor hearing

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

Consumer comments

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

2 NPWP Consideration

2.1 The Nutritional Products Working Party (NPWP) noted that the pre-PBAC response from the November 2017 PBAC meeting. In the response, the NPWP noted that PKU Baby[®], as one of the appropriate comparators contains the same level of iron as PKU Start[®].

2.2 During its consideration, the NPWP noted the low iron level in both PKU Baby[®] and PKU Start[®]. The NPWP also acknowledged the limited options of PKU products for infants in the Australian market.

2.3 The NPWP supported the Restricted Benefit listing of PKU Start[®], on the basis of a similar level of iron in the listed comparator, but remained concerned at the insufficient level of iron in both PKU Start[®] and PKU Baby[®]. The NPWP advised that the Department should write to the relevant professional organisation (i.e. the Australian Society for Inborn Errors of Metabolism) and provide appropriate information on the need to provide another source of iron to infants prescribed both PKU Baby[®] and PKU Start[®]. If listing is recommendation at the March 2018 PBAC meeting, the NPWP also suggested that an additional note should be included in the Administrative Advice to advise relevant prescribers that PKU Start[®] contains sub-

optimal iron for infants aged 7-12 months and that this should also flow on to the current listing for PKU Baby®.

3 PBAC Outcome

- 3.1 The PBAC decided to defer its decision on whether to recommend the listing of amino acid formula with vitamins, minerals and long chain polysaturated fatty acids, without phenylalanine for the dietary management of Phenylketonuria (PKU) due to the concerns on the insufficient iron level. The PBAC requested advice from the Australasian Society for Inborn Errors of Metabolism regarding the clinical need for the requested listing. The PBAC considered that this advice should be considered by the Nutritional Products Working Party (NPWP) prior to the PBAC finalising its decision.
- 3.2 The PBAC noted that the Nutritional Products Working Party (NPWP) considered the pre-PBAC response from the sponsor for the November 2017 meeting submission and provided further advice to it. The NPWP advised that there remained significant concerns at the insufficient level of iron in both PKU Start® and one of its nominated comparators, PKU Baby®.
- 3.3 The PBAC requested that the Department seek advice from the Australasian Society for Inborn Errors of Metabolism regarding whether there is a clinical need to retain the current listing for PKU Baby® and for a new listing for PKU Start® on the PBS. Input regarding to the matter from the Society and the sponsors of PKU Start® and PKU Baby® are expected before the next NPWP and PBAC meeting.
- 3.4 The PBAC noted that this submission is not eligible for an Independent Review as it has been deferred for further discussion.

Outcome:

Deferred

4 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.

5 Sponsor's Comment

The sponsor wishes to emphasise that PKU Start® is not designed to be fed as a sole source of nutrition to infants with PKU and that supplemental intake from breast milk or standard

infant formula is provided for infants from birth. From six months onwards a second stage protein substitute, solid food and/or standard infant formula is standard clinical practice in the dietary management of infants with PKU and this practice ensures all nutritional requirements are met, including iron.

In summary, Vitaflo Australia Pty Ltd acknowledges the support for the Restricted Benefit Listing of PKU Start® by the PBAC and the NPWP and is confident of its' clinical appropriateness and its' clinical need in Australia.

Addendum to the November 2017 and March 2018 PBAC Minutes:

3.01 AMINO ACID FORMULA WITH VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS, WITHOUT PHENYLALANINE

**Oral powder 400 g (PKU Start),
PKU Start®, Vitaflo Australia Pty Ltd**

AMINO ACID FORMULA WITH FAT, CARBOHYDRATE, VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE AND SUPPLEMENTED WITH DOCOSAHEXAENOIC ACID

**Oral liquid 500 mL, 20 (PKU Baby),
PKU Baby®, Orpharma Pty Ltd**

1 Background

- 1.1 At its March 2018 meeting, the PBAC decided to defer its decision on whether to recommend the listing of amino acid formula with vitamins, minerals and long chain polysaturated fatty acids, without phenylalanine (PKU Start®) for the dietary management of Phenylketonuria (PKU) due to the concerns on the insufficient iron level. The PBAC requested advice from the Australasian Society for Inborn Errors of Metabolism regarding the clinical need for the requested listing and the clinical need to retain the current listing for PKU Baby®, a nominated comparator to PKU Start®. The PBAC considered that the Nutritional Products Working Party (NPWP) should review this advice prior to the PBAC finalising its decision.

- 1.2 No response was received from the Australasian Society for Inborn Errors of Metabolism; however, the Sponsor(s) of PKU Start® and PKU Baby® were invited to respond to the NPWP and PBAC concerns regarding the iron content of their products. The NPWP considered these responses at its May 2018 meeting and provided advice to the PBAC (detailed below).

2 Sponsor responses

Vitaflo Australia Pty Ltd (PKU Start®)

- 2.1 The sponsor noted that PKU Start® complies with all requirements for foods for special medical purposes per the Food Standards Australia and New Zealand (FSANZ) Food Standards Code – Standards 2.9.5 (Foods for Special Medical Purposes) and 2.9.1 (Infant Formula Products for Specific Dietary Use). The sponsor argued that PKU Anamix Infant® is primarily the product of choice in dietary management of infant phenylketonuria (PKU) and key opinion leaders have expressed the need for availability of an alternative supply of a powdered PKU infant formula.
- 2.2 The sponsor acknowledged that without other sources of nutritional intake, PKU Start® provides 70% of the recommended daily intake (RDI) of iron, however argued the product is not designed to be the only source of nutrition for an infant with PKU and that it is not standard clinical practice to do so. The sponsor contended that, when used as part of dietary management for infant PKU, in the recommended manner, iron requirements are adequately met.
- 2.3 The sponsor also argued that when PKU Start® is used in combination with a second-stage protein substitute, such as PKU Gel®, infant iron requirements are also met. The sponsor further argued that at approximately 6 months' of age, infants would start to transition to such second-stage protein substitutes and/or solid food whilst reducing their use of PKU infant formulas, and that as such, iron intake requirements would be adequately met as patients transitioned to later-stage products.

Orpharma Pty Ltd (PKU Baby®)

- 2.4 The sponsor argued that PKU Baby® provides a nutritionally sound treatment option for infants from birth to 12 months' age, and contended that PKU infants are encouraged to be breastfed or given standard infant formula that provides additional sources of iron in addition to PKU infant formula.
- 2.5 For infants aged 7-12 months', the sponsor argued that these patients receive iron from additional dietary sources, following the introduction of a second-stage protein substitute (such as PKU Gel® or PKU Go®) and/or an iron-fortified baby cereal as solid food is commenced. The sponsor noted the previous NPWP advice that a second-stage protein supplement is generally started later in Australia (paragraph 5.4 above refers). They argued that the exact starting age of these supplements may

vary in clinical practice, depending on the dietitian involved, and argued that from 6 months' onwards, infant PKU formulas are progressively reduced, and as second-stage supplementation or solid food is introduced, sufficient iron is received from PKU Baby® as this is supplemented by additional sources.

3 NPWP Consideration

- 3.1 The Nutritional Products Working Party (NPWP) reviewed the sponsor responses to its concerns regarding the iron content of PKU Start® and PKU Baby®. They considered that there remains a high clinical need to retain PKU products on the PBS and to have a range of alternative baby and infant PKU formulas available to address the risk of shortage of one or more products.
- 3.2 The NPWP did not accept the argument(s) put forward by the sponsors regarding the use of second-stage protein supplements with higher iron intake in the 6-12 month age range, as the timing of their introduction was generally later in Australia than in other jurisdictions, such as the United Kingdom.
- 3.3 However, owing to the clinical need to ensure supply of PKU Baby® and infant formulas, the NPWP was supportive of retaining the current listing of PKU Baby® and the new listing of PKU Start®. The NPWP advised that a cautionary note should be added to the current PBS restriction for PKU Baby® (and applied to a listing of PKU Start®) to inform prescribers of the below RDI level of iron in these products.

4 PBAC Outcome

- 4.1 The PBAC recommended the Restricted Benefit listing of PKU Start® for the dietary management of phenylketonuria (PKU) on a cost-minimisation basis with PKU Anamix Infant®, at an equivalent price per gram of protein equivalent. In making this recommendation, the PBAC noted that PKU Baby® was also listed on this basis.
- 4.2 The PBAC also recommended the retention of PKU Baby® on the PBS.
- 4.3 The PBAC recommended the equi-effective doses were one gram of protein in PKU Start® is equivalent to one gram of protein in PKU Anamix Infant®.
- 4.4 The PBAC did not accept the arguments by the sponsor(s) of either PKU Start® or PKU Baby® concerning the timing of initiation of a second stage protein supplement in Australia, and agreed that both products provided an iron level below recommended daily intake (RDI) for that age group.
- 4.5 However, the PBAC also agreed with the NPWP that there was a clinical need to ensure ongoing availability of infant PKU products on the PBS, and to ensure the availability of multiple brands in case of a shortage of these products.
- 4.6 On balance, the PBAC considered that due to the clinical need it was appropriate to recommend the listing of PKU Start® for PKU. However, they agreed with the NPWP

that an administrative note regarding the sub-RDI level of iron was appropriate to ensure prescribers were aware that iron intake from other sources would be required for infants being treated with PKU Start[®]. The PBAC also recommended the same administrative note be applied to the current listing of PKU Baby[®] for the same reason.

- 4.7 The PBAC advised that similar to its previous recommendations for infant PKU products, PKU Start[®] should not be treated as interchangeable on an individual patient basis with any other drugs.
- 4.8 The PBAC advised that the PKU Start[®] brand of amino acid formula is suitable for prescribing by nurse practitioners, similar to the existing listings of PKU Baby[®] and PKU Anamix Infant[®].
- 4.9 The PBAC recommended that the Early Supply Rule should not apply as it has been the PBAC's view that general nutrients be exempt.
- 4.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

PKU Start[®] brand – New listing – Recommended

PKU Baby[®] brand – amend listing - Recommended

5 Recommended listing

5.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
AMINO ACID FORMULA WITH VITAMINS, MINERALS AND LONG CHAIN POLYUNSATURATED FATTY ACIDS WITHOUT PHENYLALANINE powder for oral liquid, 400 g	8	5	PKU Start®	Vitaflo Australia 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
Administrative advice	<i>The level of iron in this product is below the recommended daily intake (RDI) for infants and should be supplemented by other sources where appropriate.</i>

5.2 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
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	2	5	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
Administrative advice	<i>The level of iron in this product is below the recommended daily intake (RDI) for infants and should be supplemented by other sources where appropriate.</i>

6 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.

7 Sponsor's Comment

The sponsor had no comment.