7.09 AMINO ACID FORMULA WITH CARBOHYDRATE, VITAMINS, MINERALS AND TRACE ELEMENTS WITHOUT PHENYLALANINE, SUPPLEMENTED WITH DOCOSAHEXAENOIC ACID
Sachets containing oral powder 33 g, 30, PKU Synergy®, Nutricia Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission requested a Restricted Benefit listing of PKU Synergy® for the dietary management of Phenylketonuria (PKU) or hyperphenylalaninaemia in children from 10 years of age or adults.

2 Background

2.1 At the July 2017 PBAC meeting, the PBAC decided to defer its decision on whether to recommend the listing of amino acid formula with carbohydrate, vitamins, minerals and trace elements without phenylalanine, supplemented with docosahexaenoic acid; for the dietary management of PKU. The PBAC considered that there was a lack of clinical data to indicate a clinical need for the product but noted the pre-PBAC response from the sponsor and considered that these responses should be considered by the Nutritional Products Working Party (NPWP) before finalising its decision (paragraph 6.1, PKU Synergy, Public Summary Document (PSD), July 2017 PBAC meeting).

2.2 At the November 2017 PBAC meeting, the Committee did not recommend the listing of PKU Synergy for the dietary management of PKU or hyperphenylalaninaemia in children from 10 years of age on the basis that the PBAC considered that there were other products with better nutritional profiles for this patient population. The PBAC advised that there was no clinical need for listing this product (paragraph 3.1, PKU Synergy, November 2017 Addendum to the July 2017 Public Summary Document (PSD), November 2017 PBAC meeting).

2.3 The Committee noted that the pre-PBAC response for the November 2017 meeting provided additional information to justify the rationale behind the requested listing. This information included anecdotal support from the sponsor's advisory board (which consisted of six metabolic dietitians from Australia and New Zealand). However, the sponsor did not provide any new clinical evidence to support its requested listing (paragraph 3.2, PKU Synergy, November 2017 Addendum to the July 2017 PSD, November 2017 PBAC meeting).

2.4 The Committee also noted the NPWP's advice that it remained unconvinced that use of the product would provide enough copper and phosphorus for patients on a relaxed

diet and considered that if the diets were sufficiently relaxed to meet requirements for these nutrients, that there was no clinical need for PKU Synergy (paragraph 3.4, PKU Synergy, November 2017 Addendum to the July 2017 PSD, November 2017 PBAC meeting). The PBAC also noted that the NPWP advised not to recommend listing the product on the PBS (paragraph 3.5, November 2017 Addendum to the July 2017 PSD, November 2017 PBAC meeting).

For more detail on PBAC's view, see section 8 PBAC outcome.

3 Requested listing

3.1 The proposed listing is outlined below and is essentially the same as that requested in the July 2017 submission.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
AMINO ACID FORMULA WITH CARBOHYDRATE, VITAMINS, MINERALS AND TRACE ELEMENTS WITHOUT PHENYLALANINE, SUPPLEMENTED WITH DOCOSAHEXAENOIC ACID oral liquid: powder for, 30 x 33 g sachets	NEW	30	2	5	PKU Synergy®	Nutricia Australia Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☒Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☐Authority Required - Streamlined
Indication: Phenylketonuria

3.2 The minor submission noted that while the suggested intake of PKU Synergy is one sachet per day, patients may consume up to two sachets per day which will provide 60%-70% of protein requirements. The PBAC previously considered that restricting the proposed treatment to one sachet a day would be potentially confusing for consumers as this is different from what is currently recommended for other amino acids supplements in this indication (paragraph 6.5, PKU Synergy, PSD, July 2017 PBAC meeting).

For more detail on PBAC's view, see section 8 PBAC outcome.

4 Comparator

4.1 The minor resubmission nominated PKU Express 20® and PKU Lophlex® as the main comparators, the nominated comparators remain unchanged from the July 2017

submission. All three products are powdered supplements and contain 20 g protein equivalent (PE) per sachet.

4.2 PKU Synergy contains 4.3 mg of phenylalanine per sachet, whereas the main comparators PKU Express 20 and Lophlex are phenylalanine free.

4.3 The PBAC previously noted that the product does not contain copper and only extremely low levels of phosphorus that are essential elements, and also lower levels of Vitamin B6 folate, biotin and niacin than its comparators, PKU Express 20 and Lophlex (paragraph 6.4, PKU Synergy, PSD, July 2017 PBAC meeting).

For more detail on PBAC's view, see section 8 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 evidence

5.3 The minor resubmission noted that no randomised comparative trials have been undertaken at this time. The minor resubmission presented one published study, which assessed the outcomes of eating behaviour, nutrient intake and mood in adults with PKU who are non-compliant in their dietary therapy, following intake of PKU Synergy.

5.4 Details of the study presented in the resubmission are provided in the table below:

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Benjamin Green et al.	Improved Eating Behaviour and Nutrient Intake in Noncompliant Patients with Phenylketonuria after Reintroducing a Protein Substitute: Observations from a Multicentre Study. Description: Twelve non-compliant PKU adults took 1 sachet (33g) of PKU SYNERGY daily for 28 days. Eating behaviours, nutrient supply, selected nutritional biomarkers and mood were assessed at day 1-3 and again at day 29-31.	Clinical study report published: 30 August 2019

Source: Appendix C of the submission, pages 1- 3

5.5 The sponsor noted that the study reported at days 1-3 of the study, natural protein intake and estimated Phenylalanine were high with low intakes of calcium, magnesium, iron, zinc, iodine and Vitamin D. The sponsor noted that after intervention (day 29-31) with PKU Synergy, the following results were reported:

- natural protein and estimated phenylalanine intake had declined,
- fat and saturated fat intakes had decreased,
- energy and carbohydrate intake remained unchanged,
- micronutrient intake increased to levels well within reference nutrient intake recommendations. Blood Vitamin B12 and Vitamin D increased by 19.8% and 10.4% respectively,
- there were also reductions in anxiety and confusion observed during the study

Clinical claim

5.6 The sponsor claimed that the study demonstrated that reintroducing a low volume, nutrient enriched protein substitute (PKU Synergy) at 1 sachet 33 g per day, delivered favourable nutritional results and potential mood benefits in non-compliant PKU patients. The sponsor also claimed that the study demonstrated no deficiencies in copper, phosphorous, vitamin B6, folate, biotin and niacin.

5.7 The sponsor maintained that PKU Synergy will enable patients who are non-compliant in their dietary therapy and patients with a higher tolerance to phenylalanine, to meet micronutrient requirements in a smaller volume of product, which may result in less wastage of current protein substitute (prescriptions), savings to the PBS and potentially better patient compliance.

Pricing considerations

5.8 The sponsor also estimated 13 (30%) of 44 patients may be non-compliant with their diets(not taking the prescribed amount of protein substitute) and these patients will switch from PKU Express 20 and PKU Lophlex to PKU Synergy.

Table 2. Estimated annual prescription and number of patients of the comparators (PKU Express 20 and PKU Lophlex Powder)

PBS code	PKU Express 20 (PBS code 1909L)	PKU Lophlex (PBS code 8804J)
Age suitability 1909L	From 3 years of age	From 8 years of age
Annual Prescriptions	296	232)
Estimated number of patients in the (based on 1patient/12 prescriptions)	25	19
Total Estimated number of patients in	44	

Source: table 5-6 of the submission

5.9 The minor resubmission proposed a dispensed price for maximum quantity (DPMQ) based on $0.76 per gram PE (at AEMP). The proposed price in comparison to the nominated comparators are presented below.

5.10 The PBAC noted the resubmission did not provide the rationale for the higher AEMP per g PE compared to the comparators.

Table 3: Calculated costs versus comparators

	PKU Synergy	PKU Express 20	PKU Lophlex
Units	30	30	30
Max Quantity of boxes	2	4	4
g PE per serve	20	20	20
Therapeutic relativity based on protein equivalent	1	1	1
Total PE for maximum quantity	1200	2400	2400
AEMP per box	$471.00	$387.37	$382.77
AEMP per Max Qty	$942.00	$1549.48	$1531.08
AEMP per g PE	$0.758	$0.646	$0.638
PTP per box	$505.97*	$404.85*	$400.26
PTP per Max Qty	$1,011.94*	$1,619.40*	$1,601.00*
Pharmacists AHI Fee	$33.21*	$54.47*	$53.83*
Dispensing Fee	$7.39	$7.39	$7.39
DPMQ	$1,052.53*	$1,681.31	$1,662.27

Source: table 7 of the submission
AHI = administrative, handling and infrastructure; DPMQ = dispensed price per maximum quantity; PTP = price to pharmacy
*Corrected based on current fees and mark-ups

Cost/patient/year: $12,630.36

5.11 The estimated cost/patient/ per year would be $12,630.36, based on a 12 scripts per patient per year at a DPMQ $1,052.53.

Estimated PBS usage & financial implications

5.12 The minor resubmission maintained that introduction of PKU Synergy into the Australian market will not result in any new patients commencing dietary therapy.

5.13 The sponsor used the prescription data from February 2019-February 2020 and estimated that 44 patients used PKU Express 20 and PKU Lophlex, assuming one patient per 12 prescriptions. This is summarised in the table below.

5.14 The July 2017 submission estimated that approximately 60% of patients currently taking PKU Express 20 or Lophlex would be non-compliant in their dietary therapy and will therefore switch to PKU Synergy.

5.15 The minor resubmission estimated a net saving to the PBS of $0 to < $10 million in Year 5 of listing, with a total net saving to the PBS of $0 to < $10 million over the first 5 years of listing. This is summarised in the table below.

Table 4 Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated patients that would swap from PKU Express 20 & PKU Lophlex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of patients currently using PKU Express 20 (100% of protein substitute)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of patients currently using PKU Lophlex (100% of protein substitute)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost (PKU Express 20 & PKU Lophlex)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of patients using PKU Synergy (100% of protein substitute)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net savings for the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: table 10-13 of the submission

5.16 As a minor submission, the financial estimates have not been independently evaluated.

For more detail on PBAC's view, see section 8 PBAC outcome.

6 NPWP Consideration and sponsor pre-PBAC Response

6.1 The NPWP was not supportive of the listing of PKU Synergy. The NPWP noted that the resubmission presented a study (Green et al., 2019[1]) where adult patients with PKU who were non-compliant in their dietary therapy, took one sachet of PKU Synergy for 28 days. The NPWP noted that the study had only nine patients with six having classical PKU and, given the short duration of the study, the long-term efficacy of PKU Synergy was unknown. The pre-PBAC Response argued that the number of patients in the trial is comparable to that of other studies in rare metabolic diseases.

6.2 The NPWP considered that the results of the study provided in the resubmission did not adequately address the NPWP and PBAC's previous concern that the product would not provide enough copper and phosphorus for patients on a relaxed diet. Further, the NPWP considered the study did not adequately support a clinical need for PKU Synergy and maintained its previous view that there were other products with better nutritional profiles for this patient population. The pre-PBAC Response argued that inadequate intakes of copper and phosphorus are not evident in the target patient population, citing studies in patients with PKU from Das et al., 2014[2]; Rohde

[1] Green B, Rahman Y, et al: Improved Eating Behaviour and Nutrient Intake in Noncompliant Patients with Phenylketonuria after Reintroducing a Protein Substitute: Observations from a Multicentre Study. Nutrients, 11: 2035, 2019

[2] Das AM, Goedecke K, et al: Dietary Habits and Metabolic Control in Adolescents and Young Adults With Phenylketonuria: Self-Imposed Protein Restriction May Be Harmful. Journal of Inherited Metabolic Disease Reports, 13: 149-158, 2014

et al., 2014[3]; and Green et al., 2019[4]. The pre-PBAC Response (p3) emphasised that PKU Synergy would provide benefits for tetrahydrobiopterin (BH4) sensitive/responsive PKU patients (blood Phe levels of 600-1200 µmol l/L at diagnosis) and non-compliant PKU patients (blood Phe levels usually >600 µmol l/L on routine monitoring) who would have relaxed diets.

6.3 The NPWP also maintained that the recommend dosing of PKU Synergy of one sachet a day may be confusing to patients with PKU as it is different from other products. The pre-PBAC Response indicated that the one sachet dosing would provide convenience for patients while supplementing the diet with key nutrients.

For more detail on PBAC's view, see section 8 PBAC outcome.

7 NPWP consideration of pre-PBAC Response

7.1 The NPWP maintained its advice that there was insufficient evidence to support a clinical need for PKU Synergy. The NPWP considered that the additional studies from Das et al., 2014; Rohde et al., 2014 and Green et al., 2019 referenced by the pre-PBAC Response did not adequately address concerns about the levels of copper and phosphorous. In particular, the NPWP noted that Rohde et al., 2014 did not specifically investigate copper and phosphorus levels of patients and that non-adherent patients in Green et al., 2019 had a numerically lower levels of phosphorus and copper and had mean and median intakes of copper that were below the UK recommended nutrient intake value. Overall, the NPWP considered there was no evidence that PKU Synergy would provide additional benefits for patients compared to the nutritional products already listed on the PBS for this patient population. Further, the NPWP considered that other PBS-listed products were more nutritionally balanced compared to PKU Synergy.

For more detail on PBAC's view, see section 8 PBAC outcome.

8 PBAC Outcome

8.1 The PBAC did not recommend the listing of PKU Synergy for the dietary management of phenylketonuria (PKU) or hyperphenylalaninaemia in children from 10 years of age. The PBAC maintained its previous view that there were other products with better nutritional profiles for this patient population and that there was no clinical need for this product.

8.2 The PBAC noted the NPWP was not supportive of the listing of the product on the PBS.

8.3 The PBAC noted the NPWP's advice that the resubmission did not adequately address previous concerns that the product would provide enough copper and phosphorus for

[3] Rohde C, Teeffelen-Heithoff A Von, et al: PKU patients on a relaxed diet may be at risk for micronutrient deficiencies. European Journal of Clinical Nutrition 68: 119-124, 2014

[4] Green B, Browne R, et al: Nutritional and Metabolic Characteristics of UK Adult Phenylketonuria Patients with Varying Dietary Adherence. Nutrients 11: 2459, 2019

patients on a relaxed diet; and if diets were sufficiently relaxed to meet requirements for these nutrients, that there was no clinical need for PKU Synergy. The PBAC also noted that the NPWP maintained its previous advice that the recommend dosing of one sachet a day may be confusing to patients with PKU as it is different from other products.

8.4 The PBAC considered the additional information provided in the pre-PBAC Response did not adequately support a clinical need for this product. The PBAC noted that the NPWP considered there was no evidence of any additional benefits of PKU Synergy compared to other products already available on the PBS.

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

Outcome:
Rejected

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.