5.13 AMINO ACID FORMULA WITH VITAMINS AND MINERALS WITHOUT VALINE, LEUCINE, ISOLEUCINE AND SUPPLEMENTED WITH ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID, Sachets containing oral powder 12.5 g, 30 (MSUD explore5) MSUD explore5, Vitaflo Australia Pty Ltd

1 Purpose of Submission

1.1 The Category 3 submission requested a General Schedule Restricted Benefit listing of amino acid formula with vitamins and minerals without valine, leucine, and isoleucine, supplemented with docosahexaenoic acid and arachidonic acid, sachets containing 12.5 g powder equivalent to 5 g protein (MSUD explore5), for the dietary management of maple syrup urine disease (MSUD).

2 Background

2.1 MSUD explore5 is a low volume, concentrated, valine, leucine and isoleucine-free protein substitute containing 5 grams of protein equivalent (PE) per sachet for the dietary management of MSUD. It is expected that MSUD explore5 will largely be used to treat infants and young children from 6 months to 5 years of age.

Registration status

2.2 The sponsor of MSUD explore5 confirmed it meets the requirements for foods for medical purposes as set out under *The Australia New Zealand Food Standards Code – Standard 2.9.5: Food for Special Medical Purposes*.

2.3 As MSUD explore5 is marketed as a nutritional product and not a therapeutic good, it is not registered in the Australian Register of Therapeutic Goods.

Previous PBAC consideration

2.4 MSUD explore5 was previously considered for the dietary management of patients with MSUD by the PBAC at its November 2019 meeting but was not subsequently listed on the PBS.

2.5 At this meeting the PBAC recommended the 'Restricted Benefit listing of the amino acid formula, MSUD explore5, for the dietary management of maple syrup urine disease (MSUD) on a cost minimisation basis with MSUD gel, at an equivalent cost per gram of protein equivalent (PE)' (paragraph 7.1, Amino acid formula with vitamins and

minerals without valine, leucine and isoleucine Public Summary Document, November 2019).

2.6 The November 2019 recommendation was rescinded by the PBAC at its November 2021 meeting noting there had not been a Notice of Intent submitted by the sponsor to progress the listing and 'that the MSUD market was small and that alternative products were available…'. (November 2021 PBAC Meeting Outcomes, Recommendations not implemented after 2 years).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The submission requested MSUD explore5 be listed under the same circumstances as MSUD gel. The requested maximum quantity for MSUD explore5 was 8 cartons, compared to the current PBS listing of MSUD gel which has a maximum quantity of 4 cartons. The maximum quantity of 8 cartons provides the same quantity of PE as the current MSUD gel listing.

3.2 The submission requested the following new listing. Suggested additions are in italics.

Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AMINO ACID FORMULA WITH VITAMINS AND MINERALS, WITHOUT VALINE, LEUCINE, ISOLEUCINE AND SUPPLEMENTED WITH ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID					
amino acid formula with vitamins and minerals without valine, leucine, isoleucine and supplemented with arachidonic acid and docosahexaenoic acid containing 5 g of protein equivalent powder for oral liquid, 30 x 12.5 g sachets	NEW	8	8	5	MSUD explore5

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners ☒Nurse practitioners
PBS Indication:	Maple syrup urine disease
Restriction Level / Method:	☒Restricted benefit

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Comparator

4.1 The previous submission considered by the PBAC in November 2019 nominated MSUD gel. The PBAC had previously considered the nominated comparator was appropriate.

4.2 The submission nominated MSUD gel as the primary comparator and MSUD cooler10 as the secondary comparator (as the latter contains DHA). The PBAC considered this to be an appropriate comparator and considered that the alternative comparators identified by the Nutritional Products Working Party (NPWP) for the treatment of MSUD would be appropriate alternate therapies.
The NPWP identified the following alternative comparators:

- MSUD Anamix Junior
- MSUD Anamix Junior LQ

4.3 The PBAC noted MSUD gel was recommended on the basis of cost minimisation (per gram of PE) to MSUD Maxamaid, and there are many other comparators which have been cost-minimised to MSUD Maxamaid, but these were not identified as alternate comparators by the NPWP.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item.

Consumer comments

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

Clinical trials

5.3 No clinical trials were presented in the submission that directly compared MSUD explore5 to the comparator.

5.4 The submission provided clinical trial data of 'A 4 week study evaluating the acceptability of PKU explore5 a new phenylalanine free protein substitute for children' to support its argument that PKU explore5 and MSUD explore5 are very similar in formulation and thus MSUD explore5 should have the same palatability of PKU explore5. The PBAC noted that PKU explore appears to have significant formulation differences compared with MSUD explore5 and is used for a different indication.

5.5 The submission cited 4 publications (Table 1) in support of the listing of MSUD explore5. The submission stated the publications show that the MSUD explore5 formula meets most of the Australian Nutrient Reference Values and has a DHA:ARA profile similar to human breast milk and infant formula making it highly suitable for infants and young children at the introduction of solids. One publication was provided to show the success of DHA and ARA supplementation in patients with a similar disease, phenylketonuria.

Table 1: References used in the submission

Author	Publication title	Publication citation
Abad-Jorge, A	The role of DHA and ARA in infant nutrition and neurodevelopmental outcomes	*Today's Dietitian.* 2008; **10**:66
Koletzko B, Lien E, Agostino C, Bohles H, Campoy C, Cetin I, Desci T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher J, Symonds M, Szajewska H, Willatts P, Uauy R and the World Association of Perinatal Medicine Dietary Guidelines Working Group.	The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation, and infancy: review of current knowledge and consensus recommendations.	*J Perinat Med*. 2008; **36**(1): 5-14
National Health and Medical Research Council and New Zealand Ministry of Health	*Nutrient Reference Values for Australia and New Zealand*	2006. Canberra, NHMRC
Agostino C, Harvie A, McCulloch D, Demellweek C, Cockburn F, Giovanni M, Murray G, Harkness RA, Riva E	A randomized trial of long-chain fatty acid supplementation in infants with phenylketonuria.	*Dev Med Child Neuro*. 2006; **48**:207-212

Source: References presented in the main submission.

5.6 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

Clinical claim

5.7 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of MSUD explore5 compared with MSUD gel. The submission provided a comparison of the nutritional profile of MSUD explore5 with MSUD gel presented as Table 2.

5.8 The PBAC advised MSUD explore5 is expected to provide a non-inferior clinical benefit for the management of MSUD compared to the comparators identified.

5.9 The submission also made claims throughout the main body relating to potential additional benefits of MSUD explore5 over the comparator. As the submission presented a cost-minimisation analysis with claim of therapeutic equivalence/ non-inferiority, the PBAC did not provide advice on the claimed potential benefits.

Table 2: Nutritional composition MSUD explore5, and nominated comparator, MSUD gel per 100 g powder.

Nutrient per 100 g powder	MSUD explore5	MSUD gel
Energy kJ kcal	1450 342	1440 339
Protein Equivalent g	40	41.7
L-Isoleucine mg L-Leucine mg L-Valine mg	-* -* -*	0 0 0
Carbohydrate g O/W sugars g	42 28	42.9 27.1
Fat g O/W saturates g O/W pufas^ g	1.5 0.7 0.5	0.05 0.0 <0.05
DHA mg	140	-
ARA mg	280	-
Vitamins		
Vitamin A RE mcg	530	600
Vitamin D3 mcg	27	14.6
Vitamin E mg	9.7	9.0
Vitamin C mg	90	63
Vitamin K mcg	27	41
Thiamin mg	1.0	1.0
Riboflavin mg	1.5	1.2
Niacin mg (mg/NE)	6.9 (31)	14 (38.2)
Vitamin B6 mg	1.1	1.1
Folic Acid mcg	230	208
Vitamin B12 mcg	3.7	2.0
Biotin mcg	23	25
Pantothenic Acid mg	7.3	5.0
Choline mg	450	279
Minerals		
Sodium mg	195	379
Potassium mg	500	938
Chloride mg	500	583
Calcium mg	1100	1083
Phosphorus mg	730	825

Nutrient per 100 g powder	MSUD explore5	MSUD gel
Magnesium mg	135	167
Trace Elements		
Iron mg	16	14
Copper mcg	0.78	0.8
Zinc mg	11	11
Manganese mg	0.25	1.7
Iodine mcg	150	138
Molybdenum mcg	40	50
Selenium mcg	31	35
Chromium mcg	30	71
Amino Acids (g)		
L-Alanine	5.06	5.11
L-Arginine	4.80	4.85
L-Aspartic Acid	6.08	6.13
L-Cystine	1.44	1.45
L-Glutamine	4.92	5.51
Glycine	4.02	4.06
L-Histidine	1.73	1.74
L-Lysine	3.61	3.65
L-Methionine	1.04	1.05
L-Phenylalanine	2.70	2.73
L-Proline	4.25	4.29
L-Serine	2.87	2.90
L-Threonine	2.59	2.61
L-Tryptophan	1.44	1.45
L-Tyrosine	2.87	2.90
L-Carnitine (mg/100 g)	44	46
Taurine (mg/100 g)	88	92

Source: Appendix 1 and 2 of the submission,

* No added Isoleucine, Leucine or Valine. These may be present in trace amounts from other ingredients (<10 mg/100 g powder, <4 mg/serving). ^ pufas – polyunsaturated fatty acids.

Economic analysis

5.10 The submission presented a cost-minimisation approach of MSUD explore5 compared with MSUD gel and MSUD cooler10, based on the same price per gram PE of $1.33 at the approved ex-manufacturer price (AEMP) (Table 3).

Table 3: Calculated costs versus comparators

	MSUD explore5	MSUD gel	MSUD cooler 10
Presentation	30 x 12.5 g sachets 150 g PE	30 x 25 g sachets 300 g PE	30 x 87 mL pouches 300 g PE
g protein equivalent (PE) per carton	(30 x 5 g PE = 150 g)	(30 x 10 g PE = 300 g)	(30 x 10 g PE = 300 g)
AEMP per carton ($)	$199.82 ($199.815)	$399.63	$399.63
g protein equivalent (PE) per maximum quantity	1200 g PE= 8 x 150 g	1200 g PE= 4 x 300 g	1200 g PE= 4 x 300 g
AEMP per maximum quantity	$199.815 x 8 = $1598.52* (1200 g PE)	$399.63 x 4 = $1598.52 (1200 g PE)	$399.63 x 4 = $1598.52 (1200 g PE)
AEMP per g PE ($)	$1.332	$1.332	$1.332
DPMQ ($)	**$1742.46**	**$1742.46**	**$1742.46**

Source: Table 1 of MSUD explore5 submission main document

* Submission table had this number as $1599.52, which, based on the preceding calculation is understood to be a typographical error. This has been updated here to $1598.52.

[a] DPMQ as at 17 October 2022

Drug cost/patient/year: $21,200.51

5.11 The estimated drug cost/patient per year would be $21,200.51 based on the proposed DPMQ of $1,742.46 and the use of 8 cartons (30 x 12.5 g sachets per carton) per 12.167 prescriptions per year.

Estimated PBS usage and financial implications

5.12 The submission used a market share approach to predict the utilisation and estimate the financial implications of MSUD explore5 against the comparator.

5.13 Table 4 presents the estimated extent of use, cost of MSUD explore5 to the PBS/RPBS and the net financial implications to the PBS/RPBS that was included in the submission.

5.14 The submission estimated no net financial impact to the PBS/RPBS for the listing of MSUDexplore5 over six years (Year 1 $0 to Year 6 $0) as the product is expected to substitute within the existing market and not impact overall utilisation.

5.15 The PBAC supported the sponsor's estimation that the new listing would not be expected to result in a change in overall utilisation or financial impact to Government.

5.16 The submission stated that MSUD explore5 has been developed to replace MSUD gel. If MSUD explore5 was PBS-listed the sponsor indicated it will request the delisting of MSUD gel.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of MSUD explore5						
Cost to PBS/RPBS less co-payment ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of MSUD gel						
Number of scripts changed listing MSUD gel	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Cost to PBS/RPBS less co-payment ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net financial implications						
Net cost to PBS/RPBS ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Vitaflo MSUD explore5 UCM Nov22

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] Assuming 12.167 per patient per year as estimated by the submission.

The redacted values correspond to the following ranges:

[1] < 500

[2] $0 to < $10 million

[3] net cost saving

5.17 As a Category 3 submission, neither the economic analysis nor the financial estimates analysis have been independently evaluated.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 NPWP Consideration

6.1 The NPWP supported the listing of MSUD explore5 as a General Schedule Restricted Benefit listing for the dietary management of maple syrup urine disease on a cost-minimisation basis to the lowest cost comparator on a price per gram of PE basis.

6.2 The NPWP advised that MSUD gel was an appropriate comparator for MSUD explore5, and MSUD Anamix Junior and MSUD Anamix Junior LQ were also alternate comparators.

6.3 The NPWP advised that MSUD explore5 is nutritionally similar to the comparators and would provide a non-inferior clinical benefit.

6.4 The NPWP advised that MSUD explore5 is interchangeable with the comparators at a prescribing level.

6.5 The NPWP agreed with the sponsor's estimation that listing MSUD explore5 on the PBS would result in a nil financial impact to the PBS/RPBS.

6.6 The NPWP noted that it would be beneficial for patients and clinicians for the sponsor to provide communications on any intent to delist the MSUD gel product as soon as possible to allow time for patients to be transitioned onto alternative products.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule Restricted Benefit listing of amino acid formula with vitamins and minerals without valine, leucine, isoleucine and supplemented with arachidonic acid and docosahexaenoic acid (MSUD explore5) for the dietary management of maple syrup urine disease (MSUD) under the same circumstances as MSUD gel, except with a maximum quantity of 8 cartons rather than 4 cartons to provide the same number of grams of PE.

7.2 The PBAC considered that MSUD explore5 should be cost-minimised to the lowest cost comparator accepted by the NPWP (MSUD gel, MSUD Anamix Junior or MSUD Anamix Junior LQ) at an equivalent price per gram of PE.

7.3 The PBAC noted and supported the NPWP advice that MSUD explore5 is nutritionally similar to the comparators and would provide a non-inferior clinical benefit.

7.4 The PBAC considered the estimated use and estimated nil net financial impact to the PBS/RPBS over 6 years to be reasonable.

7.5 The PBAC considered that MSUD explore5 is interchangeable with the comparators (MSUD gel, MSUD Anamix Junior and MSUD Anamix Junior LQ) at a prescribing level.

7.6 The PBAC advised the MSUD explore5 is suitable for prescribing by nurse practitioners.

7.7 The PBAC recommended that the Early Supply Rule should not apply, as it has been the PBAC's view that general nutrients be exempt.

7.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because MSUD explore5 is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over MSUD gel, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AMINO ACID FORMULA WITH VITAMINS AND MINERALS, WITHOUT VALINE, LEUCINE, ISOLEUCINE AND SUPPLEMENTED WITH ARACHIDONIC ACID AND DOCOSAHEXAENOIC ACID					
amino acid formula with vitamins and minerals without valine, leucine, isoleucine and supplemented with arachidonic acid and docosahexaenoic acid containing 5 g of protein equivalent powder for oral liquid, 30 x 12.5 g sachets	NEW	8	8	5	MSUD Explore5
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners				
	Restriction type: ☒Restricted benefit				
	Indication: Maple syrup urine disease				

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

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.