

## 5.19 HIGH FAT FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS AND LOW IN PROTEIN AND CARBOHYDRATE, Oral liquid, 250 mL, 30, KetoVie 4:1, KetoVie 3:1, KetoVie Peptide 4:1, Cortex Health Pty Ltd

### 1 Purpose of Application

1.1 The minor submission requested a:

- General Schedule, Restricted Benefit listing of high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (KetoVie 3:1 and KetoVie 4:1) for ketogenic diet; and
- General schedule, Authority Required (STREAMLINED) listing of high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (KetoVie Peptide 4:1) for ketogenic diet.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients requiring a ketogenic diet for intractable seizures or because they have a glucose transport protein defect or a pyruvate dehydrogenase deficiency.
Intervention	KetoVie 4:1, KetoVie 3:1, KetoVie Peptide
Comparator	KetoCal 4:1
Outcomes	Seizure frequency (Patients with a $\geq 50\%$ reduction in seizure frequency) Adverse event frequency (including constipation, diarrhoea, nausea, vomiting, hypoglycaemia, unintended weight change)
Clinical claim	In children and adults requiring a ketogenic diet due to intractable seizures or another indicated condition, KetoVie provides an important supplement that supports ongoing use of the ketogenic diet to reduce seizure frequency.

Source: Table 1.1.1, p6 of the submission.

### 2 Background

#### **Registration status**

2.1 The Sponsor confirmed the products meet 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*.

### Previous PBAC consideration

2.2 KetoVie products have not previously been considered by the PBAC for ketogenic diet.

### 3 Requested listing

3.1 The submission proposed the following new listing. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>medicinal product pack</b>					
HIGH FAT FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS AND LOW IN PROTEIN AND CARBOHYDRATE  high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (4:1 ratio medium chain fat to carbohydrate plus protein) liquid, 250 mL, 30	NEW	6	6	5	KetoVie 4:1
high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (3:1 ratio medium chain fat to carbohydrate plus protein), liquid, 250 mL, 30.	NEW	6	6	5	KetoVie 3:1
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Indication:</b> Ketogenic diet					
<b>Clinical criteria:</b>					
Patient must have intractable seizures requiring treatment with a ketogenic diet; or					
Patient must have a glucose transport protein defect; or					
Patient must have pyruvate dehydrogenase deficiency.					
<b>Prescribing Instructions:</b> <i>This product must only be used under strict supervision of a dietitian, together with a metabolic physician and/or neurologist.</i>					
<b>Administrative Advice:</b> Authorities for increased maximum quantities, up to a maximum of 11, may be authorised.					

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
HIGH FAT FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS AND LOW IN PROTEIN AND CARBOHYDRATE  high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (4:1 ratio medium chain fat to carbohydrate plus protein) liquid, 250 mL, 30	NEW	6	6	5	KetoVie Peptide 4:1
<b>Restriction Summary [New] / Treatment of Concept: [New]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code] <input checked="" type="checkbox"/> Restricted benefit (if no price premium awarded) <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online) (if price premium awarded)					
<b>Indication:</b> Ketogenic diet					
<b>Clinical criteria:</b>					
Patient must have intractable seizures requiring treatment with a ketogenic diet; or					
Patient must have a glucose transport protein defect; or					
Patient must have pyruvate dehydrogenase deficiency.					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must require enteral tube feeding; or					
Patient must have severe intestinal malabsorption of <del>be intolerant to</del> whole protein ketogenic diet formula.					
<b>AND</b>					
<b>Clinical criteria</b>					
Patient must have unsuccessfully trialed at least one of the PBS listed ketogenic products.					
<b>Prescribing Instructions:</b>					
This product must only be used under strict supervision of a dietitian, together with a metabolic physician and/or neurologist.					
<b>Administrative Advice:</b> Authorities for increased maximum quantities, up to a maximum of 11, may be authorised.					
<b>Administrative Advice:</b> [if 'Authority Required – immediate assessment' is recommended] Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

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

## 4 Comparator

- 4.1 The minor submission nominated KetoCal 4:1 (PBS item code 9446E), KetoCal 3:1 (PBS item code 2652N) and KetoCal 4:1 LQ (PBS item code 10185C) as the main comparators. KetoCal 4:1 and KetoCal 3:1 are both powdered formulations requiring reconstitution and KetoCal 4:1 LQ is an oral liquid formulation, whereas all KetoVie products are ready to drink formulations.

4.2 The minor submission estimated the energy equivalent content of KetoVie and KetoCal formulations per maximum PBS quantity (Table 2). The submission noted the energy equivalents of each of the nutritional products for ketogenic diet varied and therefore the substitution of KetoVie for currently listed products was based on substitution of the same energy equivalent content, rather than pack sizes, or on individual or mean patient usage data.

**Table 2: Energy equivalent content of KetoVie and KetoCal**

Brand Name	PBS Item number	Kilojoules per PBS maximum quantity (g)
<b>KetoCal 4:1</b>	9446E	208,584
<b>KetoCal 4:1 LQ</b>	10185C	198,400
<b>KetoCal 3:1</b>	2652N	207,864
KetoVie 4:1	-	293,760
KetoVie 3:1	-	196,020
KetoVie Peptide 4:1	-	280,980

Source: Table 4.2.2 of the submission.

4.3 The PBAC previously accepted a cost minimisation approach for listing products for ketogenic diet, when recommending Keyo<sup>®</sup> at the same approved ex-manufacturer price (AEMP) per kJ as KetoCal 4:1 LQ<sup>®</sup> (para 6.8, Keyo Public Summary Document, November 2016 PBAC Meeting). Keyo is listed at an AEMP of \$0.0038 per kJ, whereas KetoCal is priced at \$0.0042 per kJ. In accordance with section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the PBAC cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The sponsor contended that Keyo was not an appropriate comparator (pre-PBAC response), because:

- Keyo is only available in the 3:1 ratio
- Keyo is a solid food, whereas KetoCal is a liquid which allows for infant formula feeding
- Keyo is not suitable for children under three years of age
- Keyo cannot be used as a sole source of nutrition for children over 10 years of age, whereas KetoCal can be used as a sole source of nutrition
- Keyo has a suboptimal nutritional profile and is deficient in some vitamins/minerals.

On this basis, the sponsor contended that KetoCal provides superior effectiveness over Keyo in a substantial proportion of patients.

*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 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 submission presented one retrospective review on the effectiveness and safety of KetoVie 4:1 in patients with refractory epilepsy and one clinical experience report of KetoVie Peptide 4:1 and KetoVie 3:1.

5.4 Details of the studies presented in the submission are provided in the table below.

**Table 3: Study and associated reports presented in the submission**

<b>Study ID/First Author</b>	<b>Citation</b>
Jennings 2018	Safety and Efficacy of a Whey Based Ketogenic Medical Food with Medium Chain Triglycerides in Individuals with Refractory Epilepsy: A Retrospective, Comparative, Multi-Centre Study. (Jennings and Spears 2018)
Cambrooke Therapeutics, data on file.	KetoVie Peptide 4:1 and KetoVie 3:1 Clinical Experience reports.

5.5 The submission reported the following outcomes from Jennings (2018) (Table 4).

Table 4: KetoVie 4:1 data comparison vs. published studies

Symptom	KetoVie 4:1 Group mean	Pooled Literature Review Data (data reported at diet initiation -17 months)	Fisher's Exact Test (*significance level = 0.05)
<b>Diet Responsive</b>		46%	
4 weeks*	74%		0.0054
3 months*	84%		0.002
<b>Seizure Freedom</b>		16%	
4 weeks	26%		0.1880
3 months	24%		0.2796
<b>Unintended Weight change</b>		14%	
Baseline 22%			
4 weeks*	33%		0.0275
3 months	20%		0.5509
<b>Constipation</b>		29%	
Baseline 48%			
4 weeks*	48%		0.0497
3 months	28%		1.0000
<b>Diarrhoea</b>		16%	
Baseline 4%			
4 weeks	11%		0.7693
3 months	4%		0.2052
<b>Nausea</b>		42%	
Baseline 0%			
4 weeks*	4%		0.0000
3 months*	4%		0.0001
<b>Vomiting</b>		14%	
Baseline 4%			
4 weeks	11%		1.0000
3 months	8%		0.5508
<b>Hypoglycaemia</b>		23%	
Baseline 0%			
4 weeks*	4%		0.0208
3 months*	0%		0.0033

Source: Table 2.2.5 of the submission.

5.6 The submission claimed early experience trial data (Cambrooke Therapeutics) of KetoVie Peptide 4:1 demonstrated effectiveness:

- 100% of new ketogenic diet therapy (KDT) starts (n=3) achieved seizure control and continued using KetoVie Peptide 4:1;
- All new KDT starts had ongoing gastrointestinal (GI) tolerance or resolved their GI issues;
- Patients transitioning from other KDT formulas (n=6) showed improved GI tolerance in 83% (5/6) and improved seizure control in 75% (3/4) of patients.

5.7 The submission also claimed early experience trial data (Cambrooke Therapeutics) of KetoVie 3:1 demonstrated effectiveness:

- 83% (n=6) reported seizure control improved or maintained with 50% experiencing periods of seizure freedom;

- All patients had a history of reflux, vomiting or constipation which was resolved with KetoVie 3:1.
- 5.8 The minor submission noted KetoVie products were suitable for individuals over one year of age for the dietary management of intractable epilepsy and other conditions where a ketogenic diet is indicated. The minor submission also noted KetoVie 3:1 may be more suitable for younger children or those who do not tolerate the 4:1 ratio.
- 5.9 The minor submission noted KetoVie Peptide 4:1 is a hydrolysed whey protein based enteral ketogenic formula, suitable for individuals with impaired GI function (including those requiring enteral tube feeding) and/or intolerance to intact proteins.
- 5.10 The submission also noted these products could be used as a sole source of nutrition. The nutrient content of the proposed products and the comparators (KetoCal) are presented in the table below.

Table 5: Nutrient contents of KetoVie and KetoCal and comparator/similar products per serve

Nutritional Information	KetoVie 4:1 (per 250 mL carton) (chocolate)	KetoVie 3:1 (per 250 mL carton)	KetoVie Peptide 4:1 (per 250 mL carton)	KetoCal 4:1 powder (per 100 g ) (vanilla)	KetoCal 3:1 (powder (per 100 g )	KetoCal 4:1 LQ (200 mL carton)
<b>Energy, protein, carbohydrate, salt, fat, fibre:</b>						
Energy (kJ)	1632	2887	1561	2897	2887	1240
Protein (g)	8.5	15.3	8.1	14.4	15.3	6.18
Carbohydrate (g)	1.1	7.2	0.9	2.9	7.2	1.22
Sugar, g	0	0.7	0	1.0	6	0.46
Sugar alcohols (g)	0	0	0	NR	NR	0.088
Salt (g)	0.7	0	1	NR	NR	NR
Fat (g)	38	25	37	69.2	0	29.6
Saturated fat (g)	23	9.3	12	26.7	25.5	4.4
Trans fat (g)	0	0.2	0.2	<0.05	NR	0
Monounsaturated fat (g)	12	11	18	22.8	22.3	16.6
Polyunsaturated fat (g)	3.9	4.2	6.6	19.7	16.6	7.4
Linoleic acid (mg)	2.3	12.7	5.85	16.2*	12.7*	NR
α-Linoleic acid (mg)	0.93	1.27	0.78	1.7*	1.27*	NR
DHA (mg)	76	116	140	110	116	110
Fibre (g)	5.2		2.6		0	NR
<b>Vitamins:</b>						
Vitamin A (mcg retinol equivalents)	225	188	225	370	525	158
Vitamin D (mcg of cholecalciferol)	6.3	6.3	6.2	10.5	12.7	4.6
Vitamin E (mg a-tocopherol equivalents)	2.8	2.8	1.9	10.7	7.9	3
Vitamin K (mcg)	30	20	30	31	55.9	11.2
Vitamin K1 (mcg)	15	20	15	NR	NR	NR
Vitamin K2 (MK-7) (mcg)	15	0	15	NR	NR	NR
Thiamine / B1 (mg)	0.5	0.3	0.4	0.7	0.7	0.3
Riboflavin / B2 (mg)	0.5	0.5	0.5	0.7	0.7	0.3
Vitamin B6 (mg)	0.5	0.3	0.5	0.7	0.7	0.3
Vitamin B12 (mcg)	0.6	0.7	0.5	1.3	1.4	0.34
Niacin (mg niacin equivalents)	6.2	5.9	5.2	4.9	11.2	4.6
Folic acid (mcg)	150	50	150	116	140	57.4
Folate, DFE (mcg)**	90	30	90	69.6	84	34.4
Pantothenic acid / B5 (mg)	1.8	2.1	1.8	2.9	2.8	1.2
Biotin (mcg)	7.5	5	7.5	19.1	13.9	8.2
Vitamin C (mg)	25	30	44	40	84	18.6
Choline (mg)	150	108	150	320	180	103
Inositol (mg)	0	20	32	19.1	153	8.2
<b>Minerals, trace elements:</b>						
Calcium (mg)	260	313	454	770	838	194
Phosphorous (mg)	260	213	323	462	559	194
Magnesium (mg)	60	38	57	107	105	15.2
Iron (mg)	4.5	3.3	4.4	8	12	49.8
Zinc (mg)	3	2	3.2	4	8.2	2.8
Manganese (mg)	0.8	0.3	0.8	0.91	0.63	0.4
Copper (mg)	0.2	0.2	0.2	0.55	0.83	0.28

Nutritional Information	KetoVie 4:1 (per 250 mL carton) (chocolate)	KetoVie 3:1 (per 250 mL carton)	KetoVie Peptide 4:1 (per 250 mL carton)	KetoCal 4:1 powder (per 100 g ) (vanilla)	KetoCal 3:1 (powder (per 100 g )	KetoCal 4:1 LQ (200 mL carton)
Iodine (mcg)	45	59	46	86.2	124	37
Molybdenum (mcg)	16	10	15	31.7	34.4	13.6
Chromium (mcg)	13	7.5	13	16.3	28.8	7.0
Selenium (mcg)	22	15	23	30	21	15.6
Sodium (mg)	260	150	382	529	315	226
Potassium (mg)	250	400	607	848	993	364
Chloride (mg)	220	376	467	799	481	340
<b>Reported amino acids:</b>						
L-Carnitine (mg)	50	33	50	NR	NR	NR
<b>Others:</b>						
Osmolality (mOsm/kg H2O)	478	153	478	170 per 100 mL (at 14.2% w/v)	100 per 100 mL (at 9.5% w/v)	260
pH	6.2	6.7	6.2	-	-	-

Source: Table 1.5.2 of the submission

\* Not reported in Australian datasheets. Taken from US summary publication available at: [https://www.neocate.com/wp-content/uploads/2017/11/2019-US\\_Nutricia-Product-Reference-Guide.pdf](https://www.neocate.com/wp-content/uploads/2017/11/2019-US_Nutricia-Product-Reference-Guide.pdf)

\*\* Assumes 60% of folic acid as fortified food is available as DFE (as per NHMRC nutrient website).

5.11 The minor submission provided no clinical evidence that demonstrated superior comparative effectiveness and safety of KetoVie Peptide 4:1 compared with the comparators.

5.12 As a minor submission the clinical evidence has not been independently evaluated.

### **Clinical claim**

5.13 The submission claimed non-inferior comparative effectiveness and safety of KetoVie products compared with KetoCal products.

5.14 The PBAC considered that the claim of non-inferior comparative effectiveness of KetoVie 3:1 and 4:1 compared with KetoCal products was reasonable.

5.15 The PBAC considered that the claim of superior comparative effectiveness and safety of KetoVie Peptide 4:1 compared with the comparators was not adequately justified.

### **Economic analysis**

5.16 The minor submission presented a cost-minimisation analysis of KetoVie 3:1 and 4:1 compared with KetoCal products based on the same price per kilojoule of \$0.0042 at the AEMP. The equi-effective doses were estimated as the same number of kilojoules per day and the comparison was based on the estimated requirement of 6280 kilojoules per day.

5.17 The sponsor requested a [REDACTED] % premium price for KetoVie Peptide 4:1 over KetoCal 4:1 with an AEMP of \$ [REDACTED] per kJ (further details on the price are provided in Table 6). The sponsor argued that the premium price was based on:

- its use in a small, more restricted population that is more expensive to treat;
- the costs of the additional elements of the formula; and
- complexity to carers of preparing the comparator formulations.

5.18 The price of the KetoVie products in comparison to the nominated comparators are presented in the below table.

**Table 6: Calculation of AEMP, DPMQ and DPMQ (co-payments removed) of KetoVie 4:1 and KetoVie 3:1, based on cost equivalence to the comparator**

Product (PBS item)	PBS pack	kJ per can/carton	AEMP	Price per kJ (AEMP)	DPMQ
KetoVie 4:1	250mL, 30	1632	\$205.62	\$0.0042	\$1,399.80
KetoVie 3:1	250mL, 30	1089	\$137.68	\$0.0042	\$939.60
KetoVie Peptide 4:1	250mL, 30	1561	\$	\$	\$
KetoCal 4:1 (9446E)	300g	8691	\$36.50	\$0.0042	\$995.82
KetoCal 4:1 LQ (10185C)	200mL, 32	1240	\$166.61	\$0.0042	\$947.49
KetoCal 3:1 (2652N)	300g	8661	\$36.50	\$0.0042	\$995.82
Keyo	100g, 48	1280	\$232.18	\$0.0038	\$793.38

Source: Table 4.2.6 and 4.2.7 of the submission; italics = added during evaluation

DPMQ = dispensed price per maximum quantity; AEMP = approved ex-manufacturer price; kJ = kilojoules

5.19 The minor submission stated that prior to the availability of KetoVie Peptide 4:1, treatment options for patients were preparation of a formula that included either amino acid or KetoCal. In comparison, the sponsor stated that KetoVie Peptide 4:1 did not require further preparation and was the only nutritionally complete peptide based ketogenic formula. The sponsor estimated total daily costs of KetoVie Peptide 4:1 and comparators (Table 7) based on:

- cost of the ingredients
- preparation time (based on 30 minutes at the average hourly wage (\$42.11),
- treatment of adverse events associated with modular feeding.

**Table 7: Estimated total daily costs with KetoVie Peptide 4:1 and comparator**

	Ingredients	Preparation	Additional healthcare resource use	Total
KetoVie Peptide	\$	\$0.00	\$0.00	\$
Complete Amino Acid Mix	\$86.46	\$21.06	\$11.41	\$118.93 \$97.87*
KetoCal 4:1 LQ containing formula	\$36.42	\$21.06	\$11.41	\$68.89 \$47.83*

Source: Table 3.2.6 of the submission, \*=total estimates excluding cost of preparation

5.20 The sponsor claimed that the lower cost of KetoVie Peptide 4:1 compared to the proposed comparators supported the cost-minimisation approach. When the cost of preparation is removed, the cost of KetoVie Peptide exceeds the cost of the KetoCal containing formula.

5.21 As a minor submission, the economic analysis has not been independently evaluated.

### ***Nutritional product cost/patient/year***

#### **KetoVie 4:1**

5.22 The estimated cost/patient per year would be \$ [REDACTED], based on 12 prescriptions per year for the maximum quantity requested at a DPMQ of \$ [REDACTED]. The actual cost will vary due to variations in individual patient needs.

#### **KetoVie 3:1**

5.23 The estimated cost/patient per year would be \$ [REDACTED], based on 12 prescriptions for the maximum quantity requested per year at a DPMQ of \$ [REDACTED]. The actual cost will vary due to variations in individual patient needs.

#### **KetoVie Peptide 4:1**

5.24 The estimated cost/patient per year would be \$ [REDACTED], based on 12 prescriptions per year for the maximum quantity requested at a DPMQ of \$ [REDACTED]. The actual cost will vary due to variations in individual patient needs.

### ***Estimated PBS usage & financial implications***

5.25 The sponsor used a market share approach to estimate the usage of KetoVie products on a per kJ basis compared with the comparators, and assumed no growth in the market.

5.26 The minor submission estimated a net cost to the PBS of \$0 to <\$10 million in Year 6 of listing, with a total net cost to the PBS of \$0 to <410 million over the first 6 years of listing. This is summarised in the below table.

Table 8: Estimated financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated financial implications of KetoVie 4:1</b>						
Estimated number of scripts	1	1	1	1	1	1
Cost to PBS/RPBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Cost to PBS/RPBS less co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
<b>Estimated financial implications for KetoVie 3:1</b>						
Estimated number of scripts	1	1	1	1	1	1
Cost to PBS/RPBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Cost to PBS/RPBS less co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
<b>Estimated financial implications for KetoVie Peptide 4:1</b>						
Estimated number of scripts	1	1	1	1	1	1
Cost to PBS/RPBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Cost to PBS/RPBS less co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
<b>Aggregate financial implication of the proposed KetoVie products</b>						
Cost to PBS/RPBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Net cost to PBS/RPBS less co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
<b>Estimated financial implications of the comparators</b>						
<b>Estimated financial implications for KetoCal 4:1 Oral powder 300 mg</b>						
Cost to PBS/RPBS	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Cost to PBS/RPBS less co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
<b>Estimated financial implications for KetoCal 3:1 Oral powder 300 mg</b>						
Cost to PBS/RPBS	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Cost to PBS/RPBS less co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
<b>Estimated financial implications for KetoCal 4:1 LQ Oral liquid 200 mL, 32</b>						
Cost to PBS/RPBS	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Cost to PBS/RPBS less co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
<b>Aggregate financial implication of the comparators</b>						
Cost to PBS/RPBS	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Co-payments	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Net cost to PBS/RPBS less co-payments	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
<b>Net total PBS impact of the listing of KetoVie</b>						
New listing	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Changed listing	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Net cost to PBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2

Source: KetoVie Attachment 5 Financial Analysis of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup><500

<sup>2</sup>\$0 to <\$10 million

<sup>3</sup>net cost saving

- 5.27 The sponsor claimed that while there was a net cost to the PBS, attributable to the higher cost of KetoVie Peptide 4:1, the cost to the healthcare system would be neutral or cost saving.
- 5.28 The submission assumed that all use of KetoVie was in place of KetoCal, however the listing of KetoVie Peptide 4:1 has the potential to replace both KetoCal and amino acid based preparations. Therefore, the financial estimates may be underestimated. The minor submission provided no estimate on the number of patients who required tube feeding for ketogenic diet in the private or public hospital system. There is a possibility these patients may switch to KetoVie Peptide 4:1 after its listing on the PBS. The usage and financial estimates for KetoVie Peptide 4:1 may be underestimated.
- 5.29 As a minor submission, the financial estimates have not been independently evaluated.

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

## **6 NPWP Consideration (and sponsor's further clarification)**

### KetoVie 4:1 and KetoVie 3:1

- 6.1 The NPWP advised that KetoCal 4:1 (PBS item code 9446E) and KetoCal 3:1 (PBS item code 2652N) were the main comparators for KetoVie 4:1 and KetoVie 3:1 respectively.
- 6.2 The NPWP advised that Keyo is a solid preparation and recommended from 3 years compared with KetoCal which is a powder or liquid and can be used as an infant formula if required.
- 6.3 The NPWP supported the listing of KetoVie 4:1 and KetoVie 3:1 for ketogenic diet on a cost-minimisation basis with the lowest cost alternative comparator.

### KetoVie Peptide 4:1

- 6.4 The NPWP supported the listing of KetoVie Peptide 4:1 for ketogenic diet with modified indication criteria.
- 6.5 The NPWP did not support the proposed restriction criteria "Patient must require enteral tube feeding" as comparators are also suitable for use for enteral tube feeding. The NPWP considered the submission provided no rationale as to why KetoVie Peptide 4:1 could not be used as an oral formulation, and advised KetoVie Peptide 4:1 should not be restricted to enteral feeding. The sponsor stated that the proposed criteria did not restrict use to enteral tube feeding only, and expected that a small amount of use would be for oral administration (pre-PBAC response).
- 6.6 The NPWP considered the proposed restriction for KetoVie Peptide 4:1 was broad. The NPWP considered in practice malabsorption rather than intolerance to whole protein occurred with alternative treatments. The NPWP advised the proposed clinical criterion 'Patient must be intolerant to whole protein ketogenic diet formula' should

be amended to ‘Patient must have severe intestinal malabsorption of whole protein ketogenic diet formula’. The NPWP also advised the restriction should include treatment criterion ‘Patient must have unsuccessfully trialled at least one of the PBS listed ketogenic products’. In the Pre-PBAC Response the sponsor agreed with the NPWP proposals on the restriction.

- 6.7 The NPWP noted the expected patient population was small.
- 6.8 The NPWP noted the sponsor requested a [REDACTED] % price premium for KetoVie Peptide 4:1 over the comparator. Regarding the method used for determining the cost of KetoVie Peptide 4:1, the NPWP considered:
- the inclusion of the cost of ingredients in pricing KetoVie Peptide was reasonable;
  - the inclusion of the cost of preparation time was not appropriate.

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

## **7 PBAC Outcome**

### KetoVie 3:1 and KetoVie 4:1

- 7.1 The PBAC recommended the General Schedule, Restricted Benefit listing of high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (KetoVie 3:1, KetoVie 4:1) for ketogenic diet.
- 7.2 Listing was recommended on a cost-minimisation basis to KetoCal based on the same price per kilojoule at the AEMP.
- 7.3 The PBAC noted the NPWP advised that KetoCal 3:1 and KetoCal 4:1 were the main comparators. The PBAC considered these comparators were appropriate.
- 7.4 The PBAC considered that the claim of non-inferior comparative effectiveness and safety of KetoVie 3:1 and 4:1 compared with KetoCal products was reasonable.
- 7.5 The PBAC noted that Keyo may be an alternative therapy. However, based on the NPWP advice (para 6.2) that Keyo is a solid preparation and recommended from 3 years compared with KetoCal which is a powder or liquid and can be used as an infant formula if required (refer para 6.2), the PBAC considered Keyo was not an alternative comparator to KetoCal.

### KetoVie Peptide 4:1

- 7.6 The PBAC recommended the General Schedule, Restricted Benefit listing of high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (KetoVie Peptide 4:1) for ketogenic diet.
- 7.7 The PBAC agreed with the NPWP advice that the inclusion of the cost of preparation time in the cost determination was not appropriate. The PBAC also noted the minor submission provided no clinical evidence that demonstrated superior comparative

effectiveness and safety of KetoVie Peptide 4:1 compared with the comparators. The PBAC considered the requested 100% price premium for KetoVie Peptide 4:1 was not well justified and PBAC recommended listing KetoVie Peptide 4:1 with a price based on the same price per kilojoule compared to KetoCal 4:1, but with additional PBS-eligibility criteria.

- 7.8 The PBAC noted the sponsor requested an Authority Required (STREAMLINED) listing. However, the PBAC advised that based on the same price per kilojoule as KetoCal 4:1, a Restricted Benefit listing would be reasonable.
- 7.9 The PBAC considered that the financial estimates were likely to be underestimated as: the submission had assumed that all use of KetoVie was in place of KetoCal, however the listing of KetoVie Peptide 4:1 had the potential to replace both KetoCal and amino acid based preparations; and the submission provided no estimate on the number of patients who required tube feeding for ketogenic diet in the private or public hospital system.
- 7.10 The PBAC advised that the proposed restriction criterion ‘Patient must require enteral tube feeding’ was not required, as the product is suitable for oral administration.
- 7.11 The PBAC advised that the restriction should include the criterion:
- “Patient must have severe intestinal malabsorption of whole protein ketogenic diet formula”.
  - “Patient must have unsuccessfully trialled at least one of the PBS listed products with the indication for ketogenic diet.”

#### KetoVie 3:1, KetoVie 4:1 and KetoVie Peptide 4:1

- 7.12 The PBAC advised the proposed maximum quantity of 6 packs with 5 repeats for all products was appropriate.
- 7.13 The PBAC advised that KetoVie products are suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because KetoVie products are not expected address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.16 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 2 new medicinal product packs as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
HIGH FAT FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS AND LOW IN PROTEIN AND CARBOHYDRATE					
high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (4:1 ratio medium chain fat to carbohydrate plus protein) liquid, 250 mL, 30 [AMT details TBC]	NEW	6	6	5	KetoVie 4:1
high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (3:1 ratio medium chain fat to carbohydrate plus protein) liquid, 250 mL, 30 [AMT details TBC]	NEW	6	6	5	KetoVie 3:1
<b>Restriction Summary [NEW]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Indication:</b> Ketogenic diet					
<b>Clinical criteria:</b>					
Patient must have intractable seizures requiring treatment with a ketogenic diet; or					
Patient must have a glucose transport protein defect; or					
Patient must have pyruvate dehydrogenase deficiency.					
<b>Prescribing Instructions:</b> This product must only be used under strict supervision of a dietitian, together with a metabolic physician and/or neurologist.					
<b>Administrative Advice:</b> Authorities for increased maximum quantities, up to a maximum of 11, may be authorised.					

8.2 Add 1 new medicinal product packs as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
HIGH FAT FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS AND LOW IN PROTEIN AND CARBOHYDRATE					
high fat formula with vitamins, minerals and trace elements and low in protein and carbohydrate (4:1 ratio medium chain fat to carbohydrate plus protein) liquid, 250 mL, 30 [AMT details TBC]	NEW	6	6	5	KetoVie Peptide 4:1
<b>Restriction Summary [New]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Restricted benefit					
<b>Indication:</b> Ketogenic diet					
<b>Clinical criteria:</b>					
Patient must have intractable seizures requiring treatment with a ketogenic diet; or					
Patient must have a glucose transport protein defect; or					
Patient must have pyruvate dehydrogenase deficiency					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have severe intestinal malabsorption of whole protein ketogenic diet formula.					
<b>AND</b>					
<b>Clinical criteria</b>					
Patient must have unsuccessfully trialled at least one of the PBS-listed products with the indication of: 'Ketogenic diet'.					
<b>Prescribing Instructions:</b>					
This product must only be used under strict supervision of a dietitian, together with a metabolic physician and/or neurologist.					
<b>Administrative Advice:</b> Authorities for increased maximum quantities, up to a maximum of 11, may be authorised.					

***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:

- Welcomes the positive recommendations for KetoVie 3:1 and KetoVie 4:1.

- Is unable to list KetoVie Peptide 4:1 at the same price per kilojoule as the other formulations due to a significantly higher ingredient/manufacturing cost, because of the novel peptide formulation.
- Maintains that KetoVie Peptide 4:1 is required for unique patient populations who are intolerant to first line therapies.
- Plans to resubmit to the PBAC for further consideration.