

**6.16 AMINO ACID FORMULA WITH VITAMINS AND MINERALS WITHOUT LYSINE AND LOW IN TRYPTOPHAN,
Sachets containing oral powder 24 g, 30,
GA Gel[®],
Sachets containing oral powder 25 g, 30,
GA Express15[®],
Vitaflo Australia Pty Limited**

1 Purpose of Application

- 1.1 The minor submission requested the Restricted Benefit listing of amino acid formula with vitamins and minerals without lysine and low in tryptophan, GA Gel[®] and GA Express15[®], herein referred to as GA Gel and GA Express, for the dietary management of pyridoxine dependent epilepsy (PDE).

2 Background

- 2.1 The Sponsor of GA Gel and GA Express 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*.
- 2.2 GA Gel and GA Express are both currently listed on the PBS as Restricted Benefits for the dietary management of proven glutaric aciduria type 1.
- 2.3 GA Gel and GA Express have not previously been considered by the PBAC for PDE.

3 Requested listing

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

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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 LYSINE AND LOW IN TRYPTOPHAN					
amino acid formula with vitamins and minerals without lysine and low in tryptophan powder for oral liquid, 30 x 24 g sachets	NEW	4	4	5	GA Gel
amino acid formula with vitamins and minerals without lysine and low in tryptophan powder for oral liquid, 30 x 25 g sachets	NEW	4	4	5	GA Express15

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

Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Restricted benefit
	Condition: Pyridoxine dependent epilepsy
	Indication: Pyridoxine dependent epilepsy –proven diagnosis of Antiquitin Deficiency
	Clinical criteria:
	Patient must have a proven diagnosis of Antiquitin Deficiency
	Treatment criteria:
	Patient must be taking a low lysine diet for PDE pyridoxine dependent epilepsy
	Treatment criteria:
	The condition must be treated by or in consultation with a metabolic physician.

- 3.2 The inclusion of the clinical criteria requiring patients to have a proven diagnosis of Antiquitin Deficiency appears to duplicate the indication; therefore, the Secretariat proposed removing this clinical criterion.
- 3.3 The submission noted the following requirements for prescribing GA Gel and GA Express: diagnosis of this deficiency should be confirmed with elevated α -AASA (commonly measured as 6PC) in plasma, urine, or CSF and at least one disease causing mutation in the ALDH7A1 (antiquitin) gene . The NPWP considered that these criteria were not required (paragraph 6.5).
- 3.4 The NPWP advised that treatment should be in consultation with a metabolic physician (paragraph 6.6).

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

4 Comparator

- 4.1 The minor submission claimed that there was no direct comparator for GA Gel and GA Express, as there are no nutritional products listed on the PBS for the dietary management of PDE.
- 4.2 The submission claimed that the dietary management for PDE, in the absence of lysine free protein substitute (GA Gel and GA Express), involves a low lysine and low protein

diet supplemented with vitamins, minerals, and trace elements. The submission therefore claimed that the closest comparator is the dietary management using a low lysine diet without the inclusion of lysine free protein substitute.

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

5 Population and disease

- 5.1 The minor submission stated that PDE is a very rare disorder that is characterised by recurrent seizures in the first weeks or months of life which are resistant to anti-epileptic medications but responsive to pharmacological doses of pyridoxine. Patients with PDE require pyridoxine therapy for life.
- 5.2 The submission claimed that there was an unmet clinical need for the dietary management of PDE.
- 5.3 The submission stated that both formulations have up to date nutritional profiles that contain vitamins, minerals and trace elements in amounts appropriate to meet most Australia Nutrient Reference Values (NHMRC 2006).
- 5.4 The Sponsor stated that GA Gel and GA Express are not a substitute for pharmacotherapy.
- 5.5 The Sponsor stated that recent communication with health care professionals in Australia involved in the medical and dietary management of patients with PDE has shown strong support for listing these products for the following reasons:
 - Current access to these formulae for patients with PDE is restrictive, which results in delayed commencement of treatment and a risk of supply and delivery error.
 - Current access to these formulae for patients with PDE is costly. This can result in delayed commencement of dietary treatment, abandonment of dietary therapy, or no attempt at dietary therapy.

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (1) via the Consumer Comments facility on the PBS website. The comment described how current access to appropriate specialised nutritional formulae for patients with PDE is extremely restricted and can result in significant delays in access.

Clinical trials

- 6.3 The submission stated that although a lysine-restricted diet as an adjunct treatment for PDE is recommended, it has not been studied in a rigorous fashion.
- 6.4 As a minor submission, no clinical trials were presented in the submission.

Drug cost/patient/year: \$18,472.60 (GA Gel) & \$27,488.60 (GA Express)

- 6.5 The submission requested the same price per gram of protein equivalent (PE) as the currently listed GA Gel and GA Express. The requested DPMQ was \$1847.26 for GA Gel, and \$2748.86 for GA Express. The submission stated that the PE for the maximum quantity for GA Gel and GA Express would remain the same as the current listings at 1200 g and 1800 g respectively.
- 6.6 The estimated drug cost/patient/per year would be \$18,472.60 for GA Gel and \$27,488.60 for GA Express (DPMQ x 10 scripts per year). This is based on the assumption in the minor submission that the average number of sachets per patient per day is three and that each patient would receive the maximum quantity (4 packs) per dispensing. Using this assumption, each patient would require 10 scripts per year. This may not occur in practice due to variations in individual patient needs.

Estimated PBS usage & financial implications

- 6.7 At year 6, the estimated number of patients was <500 and the net cost to the PBS would be \$0 to < \$10 million. This is summarised in Table 1 below as well as the expected patient and prescription numbers.

Table 1: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use: GA Gel						
Number of patients treated	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of scripts dispensed ^a	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated extent of use: GA Express						
Number of patients treated	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of scripts dispensed ^b	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated financial implications of GA Gel						
Cost to PBS/RPBS	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Co-payments	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Cost to PBS/RPBS less co-payments	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Estimated financial implications for GA Express						
Cost to PBS/RPBS	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Co-payments	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Cost to PBS/RPBS less co-payments	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²
Net financial implications						
Net cost to PBS/RPBS	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²	\$ ■ ²

^a Assuming 9.13 per patient per year as estimated by the submission.

^b Assuming 9.13 per patient per year as estimated by the submission.

Source: Estimated number of patients treated and net costs to PBS over next 6 years for GA Gel and GA Express from Minor Submission main body and cost minimisation excel spreadsheet for GA Gel and GA Express

The redacted values correspond to the following ranges:

¹ <500

² \$0 to < \$10 million

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

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

7 NPWP Consideration

7.1 The NPWP noted that there was no direct comparator for GA Gel and GA Express, and accepted that the closest comparator was the dietary management of PDE using a low lysine diet without the inclusion of lysine free protein substitute.

7.2 The NPWP noted that PDE is treated as a metabolic condition, with a low lysine diet the cornerstone of treatment, along with pyridoxine. GA Gel and GA Express 15 have already been reviewed and PBS listed for dietary management of Glutaric aciduria type 1, which is treated with a low lysine diet.

7.3 The NPWP noted limited research has been conducted on PDE prevalence. Research from the Australasian Society for Inborn Errors of Metabolism (ASIAM) found that approximately 1-2 patients per state in Australia had PDE. On this basis, the NPWP considered that the number of eligible patients may be higher than estimated, although the population is likely to be small.

- 7.4 The NPWP considered that the script numbers were likely underestimated, in part due to the underestimated eligible population. Additionally, the NPWP noted some patients treated only with pyridoxine may be encouraged to trial diet modification if GA Gel and GA Express were listed on the PBS, resulting in a greater number of treated patients and prescriptions.
- 7.5 The NPWP considered that GA Gel and GA Express should be prescribed in consultation with a metabolic physician and advised that this should be included in the restrictions.
- 7.6 The NPWP noted the additional requirements for prescribing GA Gel and GA Express proposed in the submission (paragraph 3.3). However, the NPWP considered that these additional requirements are not necessary, as prescribing in consultation with a metabolic physician would ensure correct interpretation of the condition. This prevents access issues for patients who may not be able to access antiquitin gene testing.
- 7.7 The NPWP supported the listing of GA Gel and GA Express for the dietary management of PDE. The NPWP considered that there was a clinical need for GA Gel and GA Express on the PBS, and that there would be minimal risk of use outside the proposed restriction.

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

8 PBAC Outcome

- 8.1 The PBAC recommended the listing of amino acid formula with vitamins and minerals without lysine and low in tryptophan, GA Gel and GA Express®, for the dietary management of pyridoxine dependent epilepsy (PDE) at the same price per gram of protein equivalent (PE) as the current listings for GA Gel and GA Express. . The PBAC noted that the protein equivalents for GA Gel and GA Express were 1200 g and 1800 g respectively per maximum quantity dispensed.
- 8.2 The PBAC noted that there were no other products currently listed on the PBS for management of PDE. The PBAC noted that the NPWP accepted that the comparator was the dietary management of PDE using a low lysine diet without the inclusion of lysine free protein substitute, and considered this was acceptable.
- 8.3 The PBAC noted that the NPWP considered that the number of eligible patients and the script numbers may be underestimated. The PBAC considered that the eligible population may be higher than estimated in the submission, however considered that the population would still be small.
- 8.4 The PBAC noted that the NPWP advised that GA Gel and GA Express should be prescribed in consultation with a metabolic physician and the additional restriction requirements suggested by the submission (para 3.3) were not necessary. The PBAC agreed with the advice of the NPWP.

- 8.5 The PBAC agreed with the NPWP that there was a high clinical need for GA Gel and GA Express for dietary management of PDE. The PBAC noted that the NPWP was supportive of the PBS listing.
- 8.6 The PBAC advised that the treatment criteria “patient must be taking a low lysine diet for pyridoxine dependent epilepsy” should be replaced with “patient must be managed on a low lysine diet for pyridoxine dependent epilepsy”.
- 8.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because amino acid formula with vitamins and minerals without lysine and low in tryptophan is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over currently listed forms of amino acid formula with vitamins and minerals without lysine and low in tryptophan, 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 2009 for Pricing Pathway A were not met.
- 8.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

9 Recommended listing

9.1 Add new 'pyridoxine dependent epilepsy' indication to the existing 'Proven glutaric aciduria type 1' indication (not shown) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
AMINO ACID FORMULA WITH VITAMINS AND MINERALS WITHOUT LYSINE AND LOW IN TRYPTOPHAN					
amino acid formula with vitamins and minerals without lysine and low in tryptophan powder for oral liquid, 30 x 24 g sachets	9438R	4	4	5	GA Gel
amino acid formula with vitamins and minerals without lysine and low in tryptophan powder for oral liquid, 30 x 25 g sachets	5484P	4	4	5	GA Express15

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

(for internal Dept. use)	Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type:	<input checked="" type="checkbox"/> Restricted benefit
	Episodicity:	[blank]
	Severity:	[blank]
	Condition:	pyridoxine dependent epilepsy
	Indication:	pyridoxine dependent epilepsy
	Treatment criteria:	Patient must be managed on a low lysine diet for pyridoxine dependent epilepsy
	Clinical criteria:	The condition must be treated by or in consultation with a metabolic physician.

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

10 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.

11 Sponsor's Comment

The sponsor had no comment.