

5.18 ARGININE

Tablet 500 mg, Arginine Easy[®], Orpharma Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested a Restricted Benefit listing for arginine for the dietary management of urea cycle disorders (UCD).

2 Requested Listing

- 2.1 The submission requested the following new listing.
- 2.2 Suggestions by the Secretariat are shown in italics and deletions are shown in strikethrough in the proposed restriction.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed for Max. Qty	Price	Proprietary Name and Manufacturer
ARGININE arginine 500 mg tablet, 300	1	5	\$5.45		Arginine Easy Orphama Pty Ltd

*corrected DPMQ

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:	Urea cycle disorders
PBS Indication:	Urea cycle disorders
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Administrative Advice	<i>Arginine is not indicated for the treatment of arginase deficiency and other inborn errors of protein metabolism.</i>
Cautions	Arginine is not indicated for the treatment of arginase deficiency and other inborn errors of protein metabolism.

3 Background

- 3.1 The sponsor of Arginine Easy[®] confirms 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*. The PBAC noted that it is possible that this product is not a food that has a medical purpose but is a therapeutic good and should be registered with the TGA. The Sponsor was requested to address this issue as to why this product should be regulated under the

The Australia New Zealand Food Standards Code — Standard 2.9.5: Food for Special Medical Purposes and not by the TGA.

- 3.2 Arginine Easy® has not been previously considered by the PBAC.
- 3.3 The minor submission indicated that Arginine Easy® tablets may be more convenient for older children and adult patients compared with the currently listed powder forms of arginine.
- 3.4 The minor submission also noted that Arginine Easy® are uncoated to allow for crushing and administration via nasogastric tubes.
- 3.5 Arginine 500® was recommended for listing by the PBAC at its March 2009 meeting and was the first arginine supplement recommended for listing by the PBAC. Currently, there are three different arginine supplements listed on the PBS (Arginine 500®, Arginine 2000® and Arginine 5000®) all in powder form.

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

4 Comparator

- 4.1 The minor submission nominated Arginine 500® as the main comparator.
- 4.2 The minor submission noted that Arginine Easy® contains a lower amount of energy (16.8 kilojoules per tablet compared with 63 kilojoules per sachet of Arginine 500®) and carbohydrate (0 grams per tablet compared with 3.3 grams per sachet of Arginine 500®). The minor submission stated that Arginine Easy® may be beneficial to patients wanting to minimise energy intake.

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 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.
 - The sponsor's proposed comparator Arginine 500® was appropriate. The NPWP also considered that Arginine 2000® and 5000® were also relevant comparators.

- One Arginine Easy® tablet contained a lower amount of energy than one sachet of Arginine 500® and considered that the tablet form of arginine may be more convenient for some patients.
 - There is a higher amount of protein equivalent in one tablet of Arginine Easy® (0.9 g) compared with one sachet of Arginine 500® (0.4 g). The NPWP noted that the submission did not contain a clinical justification for the higher protein equivalent concentration compared to Arginine 500®. The NPWP was concerned that the high amount of protein equivalent may prove detrimental to patients on highly restricted protein diets and may result in protein overload or the removal of other sources of protein from the diet.
- 5.5 The NPWP did not support the request to list Arginine Easy® for the dietary management of urea cycle disorders. The NPWP noted that the sponsor did not compare the total protein content between Arginine Easy® and its comparator in the submission. Based on the nutritional content data provided in the submission attachments, the NPWP noted that Arginine Easy® contains 0.9 g protein per tablet, which is a significant increase in total protein content over the comparator especially for patients with urea cycle disorders who are on a restrictive diet. The NPWP has requested that the sponsor provide a response on the clinical evidence to support this increase in total protein over the comparator.

Estimated PBS usage & financial implications

- 5.6 The minor submission proposed an AEMP of \$ [REDACTED] per pack based on an equivalent cost per gram of arginine compared with Arginine 500®. The minor submission calculated the DPMQ to be \$ [REDACTED]. The Department noted that this was not correct as superseded mark-up fees were used in the calculation, use of the current fees resulted in a corrected DPMQ of \$ [REDACTED].
- 5.7 The submission stated that the listing of Arginine Easy® is expected to be cost neutral to the PBS as it is a substitute for the current PBS listed Arginine 500® and priced at the same cost per gram of arginine. However, the Secretariat notes that the increased maximum quantity per prescription would result in a small cost to the PBS from substitution of Arginine 500® due to a lower patient co-payment contribution. Substitution for the both Arginine 2000® and Arginine 5000® is also possible. This would result in an increase in the cost to the PBS as the Arginine 2000® and Arginine 5000® tablets have a lower price per gram arginine than Arginine 500®.

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 arginine for the dietary management of urea cycle disorders. The PBAC considered there was a lack of clinical justification for the higher protein content compared to the comparator. The PBAC also noted that the product may come under the definition of a therapeutic good in the *Therapeutic Goods Act 1989* and may

therefore be required to be registered with the TGA. The PBAC noted that the pre-PBAC response from the sponsor attempted to address these issues and noted that the response should be considered by the Nutritional Products Working Party (NPWP) before finalising its decision.

- 6.2 The PBAC noted that the NPWP supported the decision of deferral on the listing of the product to allow the sponsor to provide justification for the issues raised above.
- 6.3 The PBAC considered that the sponsor's proposed comparator, Arginine 500[®] was appropriate however the PBAC considered that Arginine 2000[®] and 5000[®] were also relevant comparators.
- 6.4 The PBAC noted that one tablet of Arginine Easy[®] tablet contained a lower amount of energy than one sachet of Arginine 500[®] and agreed with the NPWP that the tablet form of arginine may be more convenient for some patients.
- 6.5 The PBAC noted the higher amount of protein equivalent in one tablet of Arginine Easy[®] (0.9 g) compared with one sachet of Arginine 500[®] (0.4 g) and considered that this may be detrimental to patients on highly restrictive protein diets.
- 6.6 The PBAC considered that input from the NPWP on the pre-PBAC response from the sponsor was required to assess whether the response adequately addressed the issues raised.
- 6.7 The PBAC noted that this submission is not eligible for 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 will continue to work with the PBAC and the Nutritional Products Working Party to address the matters raised in the pre-PBAC advice.

Addendum to the November 2017 PBAC Minutes:

4.03 ARGININE

Tablet 500 mg, Arginine Easy[®], Orpharma Pty Ltd

1 Purpose of reconsideration

- 1.1 At the November 2017 PBAC meeting, the PBAC noted the NPWP advice and considered there were numerous issues raised by the NPWP, which the sponsor responded to in its Pre-PBAC response. The Committee decided to defer their decision on Arginine Easy to allow for consideration of the Pre-PBAC response by the NPWP.
- 1.2 A summary of the issues raised during the previous consideration of Arginine Easy and the sponsor's response are presented in the table below.

Table 1. Issues raised during the previous PBAC consideration

Issue responded to in Pre-PBAC response	NPWP Comment	Pre-PBAC Response	PBAC Comments
Quantity of protein equivalent with comparator(s)	The NPWP noted that Arginine Easy contains a significantly higher amount of protein equivalent per 500 mg arginine (0.9g) than the comparator (0.4g), which is not clinically justified, especially for patients with urea cycle disorders who are also on protein restrictive diets.	The sponsor provided clinical advice from a clinician in Sweden noting that for a 50kg patient, protein supplementation would be safe in a range of 5-15 arginine tablets per day. The tables in the Pre-PBAC response claim that even at the maximal dose of arginine (at mean weight), the intake of protein provided by Arginine Easy would not exceed ~50% of the recommended daily protein intake in any age/gender group.	The PBAC considered the input of the NPWP would be informative on the Pre-PBAC response to this issue.
Requested maximum quantities (Minor OVR 2.4)	N/A	The sponsor argued that arginine may be administered in doses of 100 mg/kg/day up to a maximal daily dose of 6 g/day, and that therefore a pack size of 300 is appropriate as it would provide a one month supply for most patients. The Pre-PBAC response did not address whether this may represent an over-supply for patients using smaller quantities of arginine.	N/A
Food standards regulation	The NPWP considered the sponsor provided a suitable comparison against 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.	The sponsor noted that the TGA Food-Medicine Interface Guidance Tool (FMIGT) was consulted in formulating the submission, and argued that Arginine Easy does not make therapeutic claims and the product is proposed to be used in the dietary management of urea cycle disorders and other inherited metabolic diseases.	The PBAC considered that Arginine Easy tablets may come under the definition of a therapeutic good under the <i>Therapeutic Goods Act 1989</i> .

For more detail on PBAC's view, see section 9 PBAC outcome.

2 NPWP Consideration

- 2.1 The Nutritional Products Working Party (NPWP) noted the sponsor of Arginine Easy® attempted to address the high protein content in Arginine EASY® by presenting clinical advice from a Swedish Clinician. The pre-PBAC response claimed that for a 50kg patient, protein supplementation would be safe in a range of 5-15 arginine tablets per day.
- 2.2 The NPWP noted that the additional protein source of the product came from L-aspartate, which was not recorded in the nutritional information table on the product label nor anywhere on the product data sheet.

- 2.3 The NPWP considered that the product could potentially contribute up to 20% of protein dietary requirement of patients with urea cycle disorders, which was not clinically justified. The NPWP remained concerned with the high protein equivalence in the product and reiterated that the protein content of the product may prove detrimental to patients on highly restricted protein diets and may result in protein overload or the removal of other sources of protein from the diet. As such, the NPWP advised the PBAC that it did not support the listing of Arginine Easy® for urea cycle disorders, and noted that other products for this condition were available and there was limited clinical need for this formulation of arginine.

3 PBAC Outcome

- 3.1 The PBAC did not recommend the listing of arginine 500 mg tablets on the basis of clinically inappropriately high and undocumented protein content in the formulation and a lack of clinical need for an additional formulation of arginine on the PBS.
- 3.2 In reaching its conclusions, the PBAC noted the advice of the Nutritional Products Working Party (NPWP), which stated that the high levels of protein in Arginine Easy, which may account for up to 20% of daily protein intake for some patients, was due to the presence of L-aspartate in the product, which was not present in the nutritional information table on the product label nor elsewhere on the product data sheet. The PBAC agreed with the NPWP that the high levels of protein in the product could be detrimental to patients on highly restricted protein diets and further complicate management of conditions which already require complex and restrictive dietary management.
- 3.3 The PBAC noted that other arginine products which do not have similarly high levels of protein are currently listed on the PBS, and considered that there was no clinical need for additional and less suitable arginine products on the PBS.
- 3.4 The PBAC noted this submission is eligible for an Independent Review.

Outcome:

Rejected

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 had no comment.