

5.14 PROTEIN FORMULA WITH CARBOHYDRATE, FAT, FIBRE, VITAMINS AND MINERALS, NUTRINI LOW ENERGY MULTI FIBRE, 8 X 500mL, Nutricia Australia Pty Ltd

1 Purpose of Application

1.1 The major submission requested a restricted benefit listing for Nutrini Low Energy Multi Fibre for the dietary management of conditions requiring a low energy enteral tube feed.

2 Requested listing

2.1 The submission’s requested listing is shown below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LOW ENERGY FORMULA WITH VITAMINS, MINERALS AND TRACE ELEMENTS CONTAINING FIBRE Oral liquid, 8 x500ml	8	5	\$ [REDACTED]	Nutrini Low Energy Multi Fibre SB

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
PBS Indication:	Dietary management of conditions requiring a low energy enteral tube feed
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
Treatment criteria:	Nutrini Low Energy Multi Fibre must be used under the strict supervision of a dietitian.
Clinical criteria:	Patient must have low energy requirements; due to reduced mobility but AND <i>Patient must have normal protein and micronutrient requirements;</i> AND <i>Patient must be unable to use a standard 1.0kcal/ml tube feed.</i>

Population criteria:	<i>Patient must be aged from 1 to 6 years inclusive.</i>
Administrative Advice	<i>This product must only be used under strict supervision of a dietitian and a paediatrician.</i>

- 2.2 The Pre-Sub-Committee Response (PSCR, p2) disagreed with the inclusion of the specified age range proposed in the restriction (1-6 years inclusive), suggesting that the product will be used in children up to and including 12 years.
- 2.3 The Nutritional Products Working Party (NPWP) noted that the proposed wording of the restriction would allow broad access beyond patients with cerebral palsy, however the clinical benefit of this product to patients with other neurodisabilities was unclear.
- 2.4 The Pre-PBAC response (p1) proposed to that the restriction be amended to restrict to children with cerebral palsy aged 1-12 years to address concerns raised by the NPWP.

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

3 Background

- 3.1 Nutrini Low Energy Multi Fibre did not require registration with the TGA as it is classified as a "Food for Special Medical Purpose" regulated under the Australia New Zealand Food Standards Code.
- 3.2 Nutrini Low Energy Multi Fibre has not been considered by the PBAC previously.
- 3.3 During the consideration of the nutritional product Nutrini Peptisorb at its meeting in March 2015, the PBAC noted that submissions seeking the addition of a new indication/s on the PBS would usually require a major submission (Public Summary Document, Nutrini Peptisorb, March 2015, paragraph 6.3). This was in the context of highly uncertain estimates of use, with the potential for the total patient pool being >600 children. The current submission is for a smaller, but still uncertain, population.

4 Clinical place for the proposed therapy

- 4.1 The proposed therapy is a ready-to-use ('closed system') nutritionally complete tube feed formula for infants and young children who have low energy needs due to decreased or impaired mobility and are receiving their nutrition via an enteral tube feed.
- 4.2 Presently, there are no PBS listed enteral tube formulas specifically for children with low energy requirements. The options currently available for such children can involve a combination of formula products and powdered supplements to meet individual energy, protein and micronutrient needs ('open system'). The submission notes that there is an inherent safety risk of contamination and dilution errors associated with preparing the tube feed in an open system, and that the use of a closed system such as Nutrini Low Energy Multi Fibre removes these risks.

- 4.3 The NPWP noted that there is uncertainty about the clinical place for this product and considered it may be used more broadly in clinical practice than proposed in the submission.

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

5 Comparator

- 5.1 The comparator is a combination of diluted standard energy enteral tube feed formula (Nutrini Multi Fibre), Paediatric Seravit (to meet micronutrient requirements resulting from dilution of standard energy feed) and skim milk powder (as required to meet protein requirements). The ESC noted that this assumes a decision has already been made to feed with a low energy diet. The ESC considered that it was unclear both from the data provided and the requested listing who would benefit from a low energy normal nutrient feed.
- 5.2 The NPWP agreed that the comparator was appropriate, but noted that the comparator is currently available to patients through subsidised schemes in state and territory hospitals, therefore patients are unlikely to be paying the whole cost of the product.

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

6 Consideration of evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The hearing acknowledged the limited data available for this product in the broader proposed restriction and reiterated that, as stated in the pre-PBAC response, the proposed use of this product will be limited to patients with cerebral palsy aged 1-12 years. The hearing noted that while the comparator is currently subsidised through state hospitals, there are currently inconsistencies and inequalities between state access. In addressing concerns around uncertain utilisation, the hearing highlighted that a minority of patients with cerebral palsy are likely to have issues with excess weight gain, therefore the usage of this product will be small. The PBAC considered that the hearing did not substantially add to the evidence presented in the submission and the pre-PBAC response.

Consumer comments

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

Clinical trials

- 6.3 The submission is based on a single 6 month longitudinal prospective feasibility study of 14 children (ages ranging from 10 months to 11 years) with spastic quadriplegic cerebral palsy (SQCP) who were administered Nutrini Low Energy Multi

Fibre via gastrostomy tube feed. The purpose of this study was to demonstrate that children exhibit normal growth on a low energy tube feed. Additional information is provided from a tolerance study comparing gastrointestinal effects of fibre enriched formula compared to non-fibre containing formula.

- 6.4 No relevant direct comparative evidence was presented between Nutrini Low Energy Multi Fibre and the comparator. The submission acknowledges that a randomised controlled trial would have provided higher quality evidence, but argues that this is not regularly conducted in the field of medical nutrition products. Given the difficulty in recruiting for paediatric studies and the relatively low prevalence of children with severe neurodisabilities, the lack of direct comparative evidence is reasonable.
- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Study	Description	Reports
Nonrandomised studies		
Vernon-Roberts et al. (feasibility study)	6 month longitudinal feasibility study investigating nutritional outcomes and general health of children with spastic quadriplegic cerebral palsy	Vernon-Roberts A et al. Gastrostomy feeding in cerebral palsy: enough and no more <i>Developmental Medicine and Child Neurology</i> Year; 2010 Vol (52)12: 1099-1105
Grogan et al. (tolerance study)	Tolerance study providing comparison of gastrointestinal effects (including stool consistency and bowel movements and laxative usage) of non-fibre containing formula versus two fibre enriched formulas (Nutrini Low Energy Multi Fibre and Nutrini Multi Fibre)	Grogan J et al. Gastrointestinal effects of two fibre enriched paediatric enteral tube feeds. <i>J Hum Nutr Diet</i> Year 2006 Vol 19: 458 – 477

Source: compiled during evaluation

- 6.6 The volume of tube feed for each child receiving Nutrini Low Energy Multi Fibre was determined by the attending dietitian in the study. This did not exceed 75% of the estimated average requirements of energy (kcal) for age. The ESC noted the following from a commentary accompanying Vernon-Roberts 2010, written by Australian experts: 'We are concerned with the authors' contention that the children with severe Cerebral Palsy 'will grow ... even on energy intakes which are 50% of estimated average requirement for normal children'. Children with cerebral palsy and other forms of Severe Neurological Impairment are heterogeneous and have serious comorbidities that complicate feeding, so that a 'one size fits all' approach is inappropriate.'¹
- 6.7 The submission presents additional supplementary evidence from survey data of dietitians, a letter of support from a study investigator and three patient case studies. This information serves to inform the clinical management algorithm and the estimated extent of use and financial implications.

¹ Somerville H, O'Loughlin E. Gastrostomy feeding in cerebral palsy: enough and no more [commentary]. *Dev Med Child Neuro* 2010; 52 (12): 1076.

- 6.8 In the feasibility study, 1 patient was lost to follow-up, 3 patients died from respiratory infection, and 2 patients dropped out as they began to feed orally. As a result, baseline and 6 month follow-up data were available only for 8 of the 14 enrolled study participants. Overall, the high rate of study drop-outs and low follow-up rates in this study had an unknown impact on the study's findings.
- 6.9 The primary outcome measures of the feasibility study are shown in the table below.

Table 2: Primary and secondary outcomes at 6 months after commencing low energy feed

Primary outcome	Secondary outcome
Increase in weight (measured in kg and z-score), mid-upper arm circumference, upper arm length, lower leg length, triceps skinfold, subscapular skinfold.	Macronutrient intake (carbohydrate, protein and fat) measured in terms of percentage of derived energy intake.
Change in body composition measured in terms of fat mass, body fat percentage, fat mass index and fat-free mass index.	Micronutrient concentrations in plasma/serum
	General health: frequency of chest infections Bowel movement frequency (per week) and medication use for relieving constipation

Source: compiled during evaluation

Clinical effectiveness

- 6.10 The results of the Vernon-Roberts et al feasibility study demonstrate that patients appear to exhibit normal growth on a low energy tube feed without an adverse impact on general health or a disproportionate increase in body fat. The results showed that there was no significant increase in fat mass index (median diff 1.21, 95% CI -1.15 to 2.94, p=0.345) or fat free mass index (median diff -1.41, 95% CI -1.15 to 2.94, p=0.249). As the sample size of the population with follow up results is low (n=8), it is difficult to determine the reliability of this outcome measure.
- 6.11 The results of the tolerance study demonstrate that Nutrini Low Energy Multi Fibre may have possible benefits in terms of relieving constipation compared to standard enteral feeding formulations that are not fibre-enriched. The strength of this evidence is limited by the size (n=7) and duration (4 weeks) of the study.
- 6.12 The NPWP considered that there may be a small number of cerebral palsy patients who would benefit from this formula.

Comparative harms

- 6.13 No assessment of comparative harms was presented. The ESC noted that three out of fourteen patients in the main clinical study died from respiratory infection within the six-month period of the study. The ESC noted the submission's claim that this was likely to be due to complications related to patients underlying conditions, but considered that given no background rate of harms was discussed and the study did not have a control group, no assessment of comparative harms was able to be conducted.

Clinical claim

- 6.14 The submission claimed that children who used Nutrini Low Energy Multi Fibre continued to grow normally without a disproportionate increase in body fat. The

strength of evidence is low due to the small sample size and high rate of drop-outs. The results of the tolerance study are not sufficiently robust to substantiate a claim for improvement in bowel habits in terms of less reliance on laxative use to relieve constipation. The NPWP and the ESC considered that there was insufficient information available in order to support the clinical claim.

- 6.15 The ESC noted that if a major submission is pursued, sufficient information on both effectiveness and harms should be available in order to assess the clinical claim.

Economic analysis

- 6.16 The submission did not provide a formal economic analysis. Instead, the submission presented a cost-comparison of Nutrini Low Energy Multi Fibre to the comparator to derive a suitable price.

Drug cost/patient/year: \$ [REDACTED].

- 6.17 The cost per patient per year is based on a patient receiving the proposed PBS quantity of 64 cartons each month. This cost will vary significantly based on the individual patient's age and energy requirements.

Estimated PBS usage and financial implications

- 6.18 This submission was not considered by DUSC.
- 6.19 The submission used a market share approach to estimate the extent of use and financial implication of Nutrini Low Energy Multi Fibre on the PBS. The main source of data was a survey of Australian dietitians working in children's hospitals and extrapolated using population data from the Australian Bureau of Statistics.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated extent of use					
Uptake rate	30%	50%	65%	80%	90%
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total number of packs*	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	-	-	-	-	-
Patient co-payment	\$ 19,950.84	\$ 33,251.40	\$ 43,226.82	\$ 53,202.24	\$ 59,852.52
Reduction in prescriptions for Paediatric Seravit	\$11,328.27	\$11,328.27	\$11,328.27	\$11,328.27	\$11,328.27
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during evaluation from Table 8 p 58 of the submission and p51 of the submission

The redacted table above shows that the number of patients treated with Nutrini Low Energy Multi Fibre is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.

- 6.20 The financial estimates presented:
- may have overestimated patient numbers as children aged under 15 years were included in the population, rather than limiting to use in children 1-6 years to align with the manufacturers recommendation;
 - were based on all patients using 2 cartons per day. This was inappropriate as dose will be highly variable between patients;
 - did not include an estimate of patients who may be on low-energy formula short-term;
 - assumed that all patients would use this product as their sole source of nutrition; and
 - assumed that all patients will pay the general co-payment. This underestimates the total net cost.
- 6.21 Given the range of uncertainties noted, it is unclear if the estimated use and financial implications presented in the submission are likely to be an under or over estimate.

Quality Use of Medicines

- 6.22 The following quality use of medicines issues were identified by the submission:
- as Nutrini Low Energy Multi Fibre is a ready-to-use nutritionally complete formula, there is no risk of dilution errors or cross contamination associated with use of multiple products; and
 - the current method for diluting standard formula and adding addition supplements is time and labour intensive for parents. This product is more convenient to prepare and administer.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of Nutrini Low Energy Multi Fibre on the PBS for children with cerebral palsy aged 1-12 years due to an uncertain definition of the patient group likely to benefit from this product and an uncertain clinical need.
- 7.2 The PBAC noted and agreed with the advice of the Nutritional Products Working Party (NPWP) that did not support the listing of Nutrini Low Energy Multi Fibre on the PBS, including:
- uncertainty about the clinical place for this product;
 - that the comparator is currently available to patients through subsidised schemes in state and territory hospitals, and thus the patient is unlikely to be paying the whole cost of the medicine;
 - the quality of the evidence provided in the submission was of a low quality and did not support the clinical claims in the submission:
 - Noting the small sample size, the trial participants were not randomised.
 - Participants were not overweight (while submission stated that the main clinical benefit was in patients who were overweight).

- Participants appeared to grow normally, without unexpected changes in body fat.
 - No evidence was provided for extrapolating the findings to all patients who may qualify for PBS subsidy
 - there is a significant risk that the estimated use in the submission may underestimate the actual patient population and that there may be use in patients where clinical benefit may not be derived, such as patients with neurological or neurometabolic disorders other than cerebral palsy. These issues about patient numbers lead to an uncertain effect on the financial implications to Government, which are most likely underestimated.
- 7.3 The PBAC noted the revised restriction in the Pre-PBAC response which proposed limiting the use of the product to patients with cerebral palsy aged 1-12 years. The PBAC noted that excessive weight gain is unlikely to be a problem for many patients with cerebral palsy and were therefore unclear about the patient group likely to benefit from the product.
- 7.4 The PBAC noted that currently, nutritional products for patients with medical conditions requiring strict dietary management including metabolic conditions and severe protein intolerance are PBS subsidised. The PBAC considered that non-modified feeds such as Nutrini Low Energy Multi Fibre are not appropriate for inclusion on the PBS.
- 7.5 The PBAC considered that the clinical evidence presented to support the proposed listing was inadequate due to the small number of patients with follow up results in the feasibility study (n=8) and the lack of comparative evidence to demonstrate the extent of benefits in terms of improved body composition. The PBAC also noted that patients in the feasibility study did not follow the clinical algorithm as presented in the submission as patients were not gaining weight too rapidly on standard energy formula at the initiation of the study.
- 7.6 The results of the tolerance study were limited by the small sample size (n=7) and short duration (4 weeks) however the results may demonstrate a benefit in relieving constipation.
- 7.7 The PBAC agreed with the ESC that sufficient information for both effectiveness and harms should be available in order to robustly assess the clinical claim.
- 7.8 The PBAC considered that due to the unclear patient group likely to use this product, the financial impact of listing this product is unknown.
- 7.9 The PBAC noted that this submission is eligible for Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Whilst Nutricia is disappointed in the PBAC outcome, we will continue to work with the PBAC on demonstrating the value of Nutrini Low Energy Multi Fibre.

Nutricia firmly believes that medical nutrition products, whether modified or non-modified, are important in the nutritional management of patients with a disease, disorder or medical condition and will continue to seek subsidised access for patients.