5.12 PROTEIN FORMULA WITH CARBOHYDRATE, FAT, VITAMINS, MINERALS AND TRANSFORMING GROWTH FACTOR BETA-2
Powder for oral liquid, 400 g, 12
Modulen® IBD,
Nestle Health Science

1 Purpose of Application

1.1 The minor submission requested a new Restricted Benefit listing of the protein formulation Modulen® IBD, for the dietary management of Crohn disease (CD).

2 Background

2.1 The sponsor of Modulen IBD 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.

3 Requested listing

3.1 The submission did not propose a detailed restriction, however requested listing of Modulen IBD as enteral nutrition in the active or remission phases of CD in adults and children over the age of 5 years. Basic information on requested quantities and prices are presented below.

Name and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
PROTEIN FORMULA WITH CARBOHYDRATE, FAT, VITAMINS, MINERALS AND TRANSFORMING GROWTH FACTOR BETA-2 12 x 400g cans	NEW	1	12	5	Modulen® IBD	Nestle Health Science

3.2 The submission requested a maximum quantity of 12 x 400g cans per prescription with 5 repeats (total 72 cans). The requested approved ex-manufacturer price (AEMP) for the maximum quantity of 12 cans was $361.56, with a dispensed price for maximum quantity (DPMQ) of $407.59.

Place in therapy

3.3 The submission proposed a treatment algorithm for enteral nutrition in paediatric CD and argued enteral nutrition should be the first-line preferred treatment option for

paediatric CD (except in limited circumstances), with pharmacotherapy indicated for use if patients do not respond to or cannot tolerate enteral nutrition.

3.4 The Gastroenterological Society of Australia (GESA) inflammatory bowel disease 2018 clinical update[1] states that exclusive enteral nutrition (EEN) (i.e. total dietary replacement with nutritional formula), has been traditionally used for induction of remission in CD over a duration of 6-8 weeks, particularly in paediatric populations. The GESA clinical update also notes use in adults has been limited by poor palatability, non-adherence, cost and a greater willingness to use steroid therapy.

3.5 Enteral nutrition is recognised as a prior treatment option for determining eligibility for PBS-subsidised biologics (infliximab) in paediatric CD, where a patient must have tried at least two of (or be contraindicated/intolerant to) prednisolone, enteral nutrition, azathioprine, mercaptopurine or methotrexate in moderate to severe paediatric CD prior to trialling infliximab. Enteral nutrition is not a prior treatment option for determining eligibility for PBS-subsidised biologics (infliximab, adalimumab, vedolizumab or ustekinumab) in adult CD.

[1] Gastroenterological Society of Australia (GESA), 2018. Inflammatory Bowel Disease – Clinical Update for General Practitioners and Physicians. Melbourne, Victoria: GESA

Nutritional Products Working Party (NPWP) advice on requested listing and place in therapy

3.6 The NPWP advised that, based on the available information, it did not support the listing of Modulen IBD on the basis there is no clinical need for this product on the PBS. The NPWP noted other mechanisms already exist through hospitals which make enteral feeding formulas for patients with Crohn's Disease (CD) available on a cost neutral basis to patients and families (i.e. at the cost of regular diet), and that these mechanisms were effective and equitable. The NPWP also noted several pharmacotherapy options were available on the PBS for induction of remission in CD.

3.7 The Pre-PBAC Response argued that hospital-based access programs are not equitable for all patients, as some patients do not have access to supply or are located in rural or remote settings where access to hospitals is difficult. Furthermore, the Pre-PBAC response argued that variation between States and Territories meant access was not consistent and equitable across the country.

3.8 The NPWP considered enteral nutrition has a place in therapy as an alternative to pharmacotherapy (primarily corticosteroids) for the induction of remission in active Crohn Disease, particularly for paediatric patients where extended periods of pharmacotherapy may be less preferable and enteral nutrition is an established first-line treatment option.

3.9 The Pre-PBAC Response noted the NPWP advice that enteral nutrition has a place in therapy as an alternative to corticosteroids and indicated a willingness to seek a PBS listing restricted to patients where the need was greatest including:

- for treatment between courses of pharmacotherapy (particularly corticosteroids) where the maximum number of courses per year recommended in clinical guidelines has been reached;
- in paediatric patients for whom corticosteroids are not suitable or not tolerated (about 30% of patients);
- in patients in whom corticosteroids are ineffective; and
- For patients in rural and remote areas with severe flare-ups who may not have immediate access to rescue therapies such as intravenous/rectal steroids or hospital-based enteral nutrition.

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

4 Comparator

4.1 The submission proposed a mixed comparator of alternative nutritional products for adult and paediatric populations. The Sponsor proposed triglycerides medium chain formula, Peptamen Junior® (PBS code 10154K), as the main comparator for the paediatric population, noting that there are currently no nutritional products on the PBS indicated for the dietary management of CD. Peptamen Junior is currently listed as a Restricted Benefit listing for the dietary management of conditions requiring a

source of medium chain triglycerides, for those with fat malabsorption due to liver disease, short gut syndrome, cystic fibrosis or gastrointestinal disorders.

4.2 For adult CD, the Sponsor nominated comparator was private market use of the protein formula Fortisip®. The proposal was based on survey results from 29 dietitians involved in the treatment of adult patients with inflammatory bowel disease (IBD) using EEN for dietary management in Australian hospitals. The submission stated that Fortisip and other nutrient formulas (Ensure Plus and Resource) are only available on the private market and within hospital and various government funding arrangements for public health services.

4.3 The appropriate comparator is uncertain. A range of enteral nutrition formulas are available on the private market and are not limited or restricted to any specific use or population. Numerous pharmacotherapies are PBS subsidised and recommended in the GESA Guidelines for CD (in certain clinical situations) including:

- Corticosteroids, such as prednis(ol)one and budesonide
- Aminosalicylates (5-ASAs), such as mesalazine
- Immunomodulators, such as azathioprine, mercaptopurine and methotrexate
- Biologics, such as infliximab, adalimumab, vedolizumab and ustekinumab
- Antibiotics (for treatment of CD complications)

4.4 Under 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 in toxicity over the alternative therapy. In this case, alternative therapies may include alternative PBS-listed pharmacotherapies for the treatment of CD and privately or hospital funded enteral nutrition formulas.

NPWP advice on comparators

4.5 The NPWP considered the submission selected incorrect comparators for both the paediatric and adult populations. For the paediatric population, the NPWP considered the nominated comparator of the triglycerides medium chain formula Peptamen Junior was inappropriate as it is specifically indicated for dietary management of fat malabsorption in a number of clinical circumstances. The NPWP considered the appropriate comparator for Modulen IBD in the paediatric population was standard enteral nutrition formula (such as Ensure or Ensure Plus) provided through the private market or through hospital distribution programs. The NPWP considered prolonged use of corticosteroids and other pharmacotherapies may be of inferior safety to enteral nutrition (including Modulen IBD) in the paediatric population (based on their known safety profiles) and therefore these were not appropriate comparators.

4.6 The Pre-PBAC Response argued that while alternative private market enteral nutrition formulas may be relevant comparators, Ensure and Ensure Plus are not marketed in

children. Furthermore, the Sponsor also argued the included evidence indicated Modulen IBD may be superior to Ensure Plus at achieving remission, as one of the included retrospective studies[2] found higher rates of remission in children (as defined by patients achieving a PCDAI[3] score of <15) with Modulen IBD compared to Ensure Plus and no enteral nutrition. However, the Sponsor stated it was amenable to considering Ensure and Ensure Plus as relevant comparators for a cost minimisation analysis.

4.7 For the adult population, the NPWP considered the nominated comparator of private market use of the protein formula Fortisip® was also inappropriate, as corticosteroids are generally effective, inexpensive, and well-tolerated in mild-moderate CD in the adult population, and furthermore that enteral nutrition is often less acceptable to adult patients due to the level of dietary restriction required. The NPWP advised it considered the most appropriate comparator for Modulen IBD in the adult CD population was the least costly PBS-listed alternative corticosteroid formulation used in the treatment of CD.

4.8 The Pre-PBAC Response acknowledged EEN is rarely used in adults as the exclusion of all other diet is less acceptable and there are frequent compliance issues in this population. The Pre-PBAC response stated Fortisip was chosen as it is on the Queensland health formulary for EEN and indicated a willingness to restrict use of Modulen IBD in adults to those are unsuitable for or have failed therapy with corticosteroids and to work with the PBAC to identify appropriate comparators for these patients.

For more detail on PBAC's view, see section 6 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 and welcomed the input from Crohn's and Colitis Australia that identified the cost of enteral nutrition as a barrier for patients, particularly for those for whom steroids are not optimal. The submission also described patient experiences of improved disease remission, reduced disease flares, reduced hospitalisations as well as improved mental health and quality of life while on and following treatment with Modulen IBD.

[2] Hartman C, *et al* (2008). Nutritional Supplementation with Polymeric Diet Enriched with Transforming Growth Factor-Beta 2 for Children with Crohn's Disease. The Israel Medical Association Journal, Volume 10, July 2008, pp 503-507.

[3] Paediatric Crohn's Disease Activity Index

Clinical evidence

5.3 The submission provided a number of references to clinical and epidemiological studies to support the effectiveness of enteral nutrition in CD, as EEN, as partial enteral nutrition (PEN) in adults and paediatric patients, and for use in the perioperative setting (i.e. prior to surgery for CD). The included evidence consisted mostly of non-randomised, open label or single-arm studies. The Pre-PBAC Response argued the totality of evidence supported a conclusion that Modulen IBD was effective to help induce and maintain clinical remission, promote mucosal healing, decrease inflammation during the active phase of disease and improve nutritional and quality of life outcomes.

NPWP advice on clinical evidence

5.4 The NPWP considered the best available evidence was a 2018 Cochrane Review of enteral nutrition for treatment of active Crohn's disease[4]. The review concluded there was very low quality evidence to suggest enteral nutrition may be more effective than corticosteroids for the induction of remission in paediatric CD. The review also found very low quality evidence to suggest corticosteroids may be more effective than enteral nutrition for the induction of remission in adult CD. The NPWP considered the findings of the Cochrane Review supported its advice regarding the place in therapy and appropriate comparators for Modulen IBD.

5.5 Further, the NPWP considered that based on the available evidence, there was no reason to conclude the addition of transforming growth factor β-2 (TGF-β-2) in Modulen IBD provided any additional benefit over alternative enteral nutrition formulas.

Economic analysis

5.6 The submission requested listing on a cost minimisation basis to Peptamen Junior and Fortisip, at an equivalent price per kcal of prepared formula.

5.7 The cost minimised price of Modulen IBD of $39.54 per can (containing 2,012kcal energy) in the paediatric population was calculated based on a price of $0.0197/kcal, derived from the approved ex-manufacturer price (AEMP) per pack of Peptamen Junior ($36.55) and energy content per pack (1,860 kcal), as shown in Table 1 below.

Table 1: Cost minimisation analysis for paediatric patients

Data	Peptamen Junior (400 g)	Modulen IBD (400 g)
Kcal per container	1860	2012
Price per kcal	$36.55/1860= $0.0197 per kcal	cost minimisation
Ex Manufacturer Price per tin	$36.55	**$39.54**

Source: table 3.3, pg 44 of the submission

[4] Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD000542. DOI: 10.1002/14651858.CD000542.pub3

5.8 The cost minimised price of Modulen IBD of $26.49 per can in the adult population was calculated based on a price of $0.01367/kcal, derived from a private market sourced price of Fortisip[5] ($3.95/unit) and energy content per pack (300 kcal), as shown in Table 2 below.

Table 2: Cost minimisation analysis for adolescent/adult patients

Data	Fortisip (200 mL)	Modulen IBD (400 g)
Kcal per container	300	2012
Price per kcal	$3.95/300 = $0.013167 per kcal	cost minimisation
Cost minimised ex-manufacturer price per tin		$26.49

Source: Table 3.4, pg. 46 of the submission

5.9 The weighted cost minimised price was calculated based on the expected proportion of use in children, adolescents and adults, as outlined in the table below, with a resultant requested AEMP of $30.13 per pack. The submission considered Fortisip to be the appropriate comparator for young adolescents (aged 11-14 years) and calculated the proposed cost minimised price using the adult price for this population.

Table 3: Weighted cost minimised price for Modulen IBD

Data	Cost-minimised price	New patients in Year 1	Proportion patients	Weighted price
Children (1-10 years)	$39.54	79	27.9%	$11.04
Young Adolescents (11-14 years)	$26.49	51	18.0%	$4.77
Older Adolescents and Adults	$26.49	153	54.1%	$14.32
Total	-	283	100.0%	**$30.13**

Source: Table 3.5, pg. 46 of the submission

NPWP advice on the economic analysis

5.10 As it considered the nominated comparators were inappropriate, the NPWP considered the cost minimisation analysis was of limited value. The NPWP noted the comparators it considered were appropriate for the paediatric and adult populations were likely to be substantially less costly over a course of treatment than the requested price of Modulen IBD. The Pre-PBAC Response indicated willingness to consider listing on a cost minimisation basis with mutually agreeable and appropriate comparators.

Drug cost/patient/course: $2,037.95 (paediatric); $2,445.54 (adolescent/adult).

5.11 The submission defined a course of treatment based on a daily energy intake of 1,903 kcal for paediatric patients (0.95 packs/day) and 2,486 kcal/day for adolescent/adult patients (1.24 cans/day). The submission defined an 8-week course of Modulen IBD as EEN as 52.97 cans for paediatric patients and 69.19 cans for adolescents and adults. Based on the requested maximum quantity of 12 cans per prescription, it was assumed paediatric patients would require 5 dispensing's and

[5] Table 3.4, pg 46 of the submission. Reference prices in submission sourced 11 December 2019 from www.pharmacyonline.com.au and www.chemistdirect.com.au.

adolescent/adult patients would require 6 dispensing's for an 8-week course of treatment at the requested DPMQ of $407.59.

Estimated PBS usage & financial implications

5.12 The submission used an epidemiological approach to estimate the extent of use of Modulen IBD under the proposed listing. The submission assumed an incidence rate of 5.0 cases per 100,000 population in children aged 5-14 and 14.61 per 100,000 population in patients aged 15 and over, and an assumption that 50% of paediatric patients and 25% of adult patients would be re-treated in the following year of estimates. The submission assumed no replacement of PBS-subsidised pharmacotherapies or Peptamen Junior, as it is only listed for patients with fat malabsorption within CD. The submission assumed 80% uptake in paediatric and adolescent populations. The submission assumed utilisation based on dietary requirements outlined in paragraph 5.9 above, and included adjustments for assumed use as PEN. A PEN course was defined as 12 weeks of treatment at 37.5% of the EEN requirements, with PEN assumed to be used for prevalent and re-treatment patients only (i.e. 50% paediatric/25% adults based the usage rate in the preceding year). The sources and assumptions in the utilisation and financial estimates were not independently evaluated.

5.13 The submission utilisation and financial estimates are presented in the table below. Totals include both incident (assumed treated as EEN) and prevalent (assumed treated as PEN) patients.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population estimates and uptake						
Eligible paediatric patients						
Eligible adolescent patients						
Uptake rate	80%	80%	80%	80%	80%	80%
Eligible adult patients						
Uptake rate	5%	5%	5%	5%	5%	5%
Estimated extent of use						
Paediatric patients treated						
Adolescent patients treated						
Adult patients treated						
Number of patients treated						
Number of scripts dispensed						
Estimated financial implications of Modulen IBD						
Cost to PBS/RPBS	$	$	$	$	$	$
Copayments	-$	-$	-$	-$	-$	-$
Cost to PBS/RPBS less copayments	$	$	$	$	$	$

Source: Compiled from Tables 4.3, 4.4, 4.5 and 4.7 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million per year.

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

6 PBAC Outcome

6.1 The PBAC did not recommend the PBS listing of protein formula with carbohydrate, fat, vitamins, minerals and transforming growth factor beta 2 (Modulen IBD) for the dietary management of Crohn Disease (CD), due to an uncertain clinical need on the PBS, inappropriate and uncertain comparators for the requested populations, and uncertain evidence of clinical benefit due to the nature and quality of the evidence presented.

6.2 The PBAC considered there was an uncertain and likely limited clinical need for enteral nutrition to be subsidised on the PBS for this population as there are a range of therapeutic alternatives on the PBS in which acceptable cost-effectiveness has been established. Furthermore, the PBAC noted mechanisms to access enteral nutrition that are cost-neutral to patients currently exist through hospital access programs and considered the arguments in the Pre-PBAC Response did not sufficiently establish a clinical need for PBS listing in a population that was not adequately met by current arrangements.

6.3 Noting the Nutritional Products Working Party (NPWP) advice, the PBAC considered that there may be a clinical place for enteral nutrition in the treatment algorithm for CD, particularly for paediatric patients where extended periods of pharmacotherapy may be associated with unfavourable safety outcomes.

6.4 The PBAC agreed with the NPWP advice that the nominated comparators were inappropriate and considered all PBS listed pharmacotherapy options and enteral nutrition formulas used for CD could be relevant comparators. The Committee noted the NPWP advice and clinical guidelines, which did not recommend the long-term use of corticosteroids or pharmacotherapy in paediatric patients and considered private market or hospital-provided enteral nutrition may be more appropriate comparators than pharmacotherapy in this population.

6.5 The PBAC noted the body of clinical evidence was generally of low quality and consisted primarily of single-arm, retrospective and/or non-randomised studies, and further noted the Cochrane Systematic Review identified by the NPWP considered the available comparative evidence to corticosteroids to also be of low quality. The PBAC considered that while the presented evidence generally supported the contention that enteral nutrition may be of some benefit for the induction and maintenance of remission in CD in some patients, it was not possible to reliably evaluate the comparative effectiveness or safety of Modulen IBD with relevant alternatives.

6.6 The PBAC agreed with the NPWP that the included cost minimisation analysis was uninformative as the nominated comparators were inappropriate.

6.7 The PBAC considered utilisation estimates to be uncertain as the uptake assumptions were arbitrary and it was unclear how Modulen IBD (and enteral nutrition more broadly) may be used in practice if listed on the PBS for the management of CD.

6.8 The PBAC advised that any resubmission should restrict the requested population to clearly defined groups in whom there is a current unmet need, which may include those outlined in the pre-PBAC response.

6.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

7 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.

8 Sponsor's Comment

The sponsor had no comment.