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GRÜNBIOTICS
Medical Nutrition. Improving Lives.

Ms Sasha Barclay
Director
Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606

GRUNBIOTICS PTY LTD
ACN: 610 953 878

Suite 211, West Podium, Level Mezzanine 2, Rialto,
525 Collins Street, Melbourne, Vic 3000, Australia

quality@grunbiotics.com www.grunbiotics.com

+613 8692-0006

Dear Ms Barclay

GRUNBIOTICS PTY LTD: NEUROFOLIN

This is a public submission and has been prepared on the basis that the Therapeutic Goods Administration intends to publish submissions in full on its website. It contains information that is appropriate for publication.

On 7 August 2019 the Therapeutic Goods Administration (**TGA**) provided us with a draft declaration which it proposes to make under s 7 of the *Therapeutic Goods Act 1989* (**Therapeutic Goods Act**). The purpose of this public submission is to provide the TGA with our comments on the draft declaration, which can be summarised as follows:

- there is a complex definitional issue with the way all FSMPs are categorised at the food-medicine interface. This issue is clearly broader than any single product and there is no principled reason why Neurofolin should be singled out when it applies to all FSMPs;
- the evidence and independent, expert opinion demonstrates that Neurofolin is a Food for Special Medical Purposes (**FSMP**) and, in those circumstances, it would be inappropriate to make a s 7 declaration in the terms proposed;
- Neurofolin is not represented as being for therapeutic use. We have recently made amendments to the presentation, claims, indication and formulation of Neurofolin that we submit put the issue of whether Neurofolin is represented in any way to be, or likely to be taken to be for therapeutic use beyond reproach;
- there is no evidence to suggest that Neurofolin is taken to be for therapeutic use;
- the draft s 7 declaration is unreasonably broad and defeats the statutory purpose of Standard 2.9.5 of the Australia New Zealand Food Standards Code (**Code**);
- there is no evidence of any health or safety issue in relation to Neurofolin and it would be inappropriate to make a s 7 declaration which would have the effect of depriving individuals who use it access to a safe and effective product.

1. A complex definitional issue that applies to all FSMPs

1.1 We believe that the proposed s 7 declaration highlights broader issues with how FSMPs are categorised at the food-medicine interface. We are extremely concerned that there is no principled reason why Neurofolin should be taken off the market when the definitional issue with FSMPs is clearly broader than any single product and applies to all FSMPs.

1.2 There is also an extensive history of Australian food regulatory agencies grappling with the complexities of regulating the food-medicine interface. In November 2007, the Food Regulation Standing Committee tasked the Addition to Food of Substances other than Vitamins and Minerals Working Group (**Working Group**) with developing a Policy Guideline for the intent of Part 2.9 – Special Purpose Foods. In a paper summarising the submissions from Food Standards Australia

New Zealand and other government and industry bodies, the Working Group remarked (at pp 21-22):

> *In maintaining clarity and consistent risk-based regulatory decisions at the food-medicine interface the submitters agreed that there is a need for more transparency and that there is a need to define those products that are to be regulated as foods and those that are more appropriately regulated by the Therapeutic Goods Administration (TGA).*

1.3 The Committee concluded that *'There are likely to be significant issues raised in addressing regulation at the food medicine interface.'*

1.4 If the TGA finds that Neurofolin is for therapeutic use, then logically all FSMPs which are designed for metabolism disorders must similarly be for therapeutic use. There are many FSMPs designed for metabolism disorders on the market, for example, PKU Nutri 1 Energy, which is specially designed for phenylketonuria.

1.5 The following table sets out some examples of comparable FSMPs which we think would be affected by the definitional issue the TGA has raised. It is by no means an exhaustive list and there are many more products marketed as FSMPs which are designed to address inborn errors of metabolism.

No.	Product	Purpose
1.	PKU Nutri 1 Energy	For the dietary management of proven phenylketonuria (PKU) in infants from birth to 12 months and as a supplementary feed up to 3 years. An amino acid based phenylalanine-free powdered infant formula containing essential and non-essential amino acids, carbohydrate, fat, vitamins, minerals and trace elements.
2.	PKU Start	PKU start is an amino acid based powdered phenylalanine free* formula containing other essential and non-essential amino acids, carbohydrate, fat, vitamins, minerals, trace elements, arachidonic acid (ARA) and docosahexanoic acid (DHA). PKU start is suitable for the dietary management of Phenylketonuria from birth.
3.	Souvenaid	A food for special medical purposes that nutritionally supports memory function during the early stages of Alzheimer's disease.
4.	GlucoControl	A pre-meal drink product that has shown significant benefit in lowering the blood glucose excursions experienced by patients after high GI meals, and also to significantly positively impact HbA1c measures versus controls in long term use.
5.	Sustagen Diabetic	SUSTAGEN® Diabetic is a Food for Special Medical Purposes specifically formulated for people with diabetes who cannot meet their nutritional needs through diet modification alone.
6.	S.O.S	A range of powdered carbohydrate drink mixes for use as an emergency regimen in the dietary management of inborn errors of metabolism. Each dose-related sachet is made up to a final volume of 200ml to provide age-specific carbohydrate concentrations.
7.	IMPACT® Advanced Recovery	Impact Advance Recovery® Drink contains a unique blend of immunonutrients (arginine, omega-3 fatty acids and dietary nucleotides) specially formulated to meet the unique nutritional needs of patients at risk of infection associated with major surgery or critical illness.
8.	Novasource	OVASOURCE® Renal is 2.0 kcal/mL with a high protein content. It is low in sodium and potassium, and lower in phosphorus for the dietary management of individuals with chronic or acute renal disease and for those requiring electrolyte restrictions.
9.	RESOURCE	RESOURCE® Fruit Flavoured Beverage is specifically formulated for the dietary management of malnutrition and other medical conditions with increased nutritional needs that cannot be met through diet modification alone.

10.	Arginaid	ARGINAID® powder is a medical food arginine module specially formulated for the dietary management of altered physiologic or metabolic conditions that respond to increased arginine intake. Arginaid® and Arginaid® Extra is a food for special medical purposes specifically formulated with L-Arginine for the nutritional management of wounds.
11.	Docomega	Powdered long chain polyunsaturated fatty acid on a carbohydrate base for the dietary management of inborn errors of metabolism. Each 4g sachet contains 200mg of docosahexaenoic acid (DHA).

1.6 Our view is that if there is an issue with the way FSMPs - including Neurofolin - are categorised, this is an issue which affects all FSMPs including, but not limited to, the examples in the table above. We cannot see any principled reason why Neurofolin should be singled out in the manner contemplated by the draft s 7 declaration which, if made, would remove Neurofolin from the Australian market.

The requirements of Standard 2.9.5

1.7 Standard 2.9.5 of the Code relates to FSMPs. Standard 2.9.5 - 2 provides:

> *(1)* *… **food for special medical purposes** means a food that is:*
>
> *(a)* *specially formulated for the dietary management of individuals:*
>
> *(i)* *by way of exclusive or partial feeding, who have special medically determined nutrient requirements or whose capacity is limited or impaired to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients in ordinary food; and*
>
> *(ii)* *whose dietary management cannot be completely achieved without the use of the food; and*
>
> *(b)* *intended to be used under medical supervision; and*
>
> *(c)* *represented as being:*
>
> *(i)* *a food for special medical purposes; or*
>
> *(ii)* *for the dietary management of a disease, disorder or medical condition.*
>
> *(2)* *Despite subsection (1), a food is not **food for special medical purposes** if it is:*
>
> *(a)* *formulated and represented as being for the dietary management of obesity or overweight; or*
>
> *(b)* *an infant formula product.*

1.8 Standard 2.9.5 - 4 specifies, relevantly, that a claim in relation to a FSMP must not refer to the prevention, diagnosis, cure or alleviation of a disease, disorder or condition.

1.9 Section 3 of the Therapeutic Goods Act defines therapeutics goods and therapeutic use. Relevantly, this includes:

> (a) "***therapeutic goods***' means goods … that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be.... for therapeutic use….'
>
> (b) "***therapeutic use***' means use in or in connection with… preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons; or … influencing, inhibiting or modifying a physiological process in persons…'

1.10 There is considerable complexity in these requirements. Although a claim in respect of a FSMP must not refer, for example, to the 'alleviation' of the disease, disorder or condition itself, a FSMP must be for the management of the diet of an individual who has a limited or impaired capacity to take, digest, absorb, metabolise or excrete certain nutrients (presumably, as a result of some disease, disorder or condition the person has), and whose dietary management cannot be completely achieved without the use of the food.

1.11 We think that this complexity, which is inherent in the very definition of FSMPs in general, is what gives rise to the Working Group's conclusion that there are likely to be 'significant issues' in regulating the food-medicine interface.

1.12 As stated above, we are concerned that there is no principled reason why Neurofolin should be taken off the market when the definitional issue with FSMPs is clearly broader than any single product and applies to all FSMPs.

2. **Neurofolin is a Food for Special Medical Purposes**

2.1 We think it is relevant in deciding whether to make a s 7 declaration for the delegate to consider whether or not there is evidence to support the conclusion that Neurofolin is a FSMP. Since June 2019, we have provided a large volume of evidence to the TGA which supports the view that Neurofolin meets the definition of a FSMP. We take each element of the definition in Standard 2.9.5 in turn.

'Specially formulated for the dietary management of individuals'

2.2 The evidence Grunbiotics has obtained and presented to the TGA consistently supports the view that Neurofolin is for dietary management as opposed to treatment. That evidence includes the following:

(a) up to 70% of patients who suffer from MDD have an inborn error of metabolism, exhibiting a genetic abnormality as a carrier of the MTHFR 677T allele, showing either a C677T heterogeneous or homogeneous polymorphism;

(b) this gene is implicated in the inability to sufficiently convert regular dietary folate, including folic acid, to L-5-methyfolate (L-5-MTHF)

(c) these patients show a markedly reduced ability to metabolise folate to L-5-MTHF, a feature not able to be addressed by intake of normal food;

(d) Neurofolin has been developed to address this dietary imbalance in those individuals suffering from MDD who also suffer from an inability to adequately metabolise folate. In other words, the inability to metabolise folate leads to a dietary requirement for this kind of nutrient, to respond to the natural inability or impairment of such individuals;

(e) the evidence suggests that it is (at the very least) very difficult to satisfy the nutritional needs of such individuals by exclusively modifying their normal diet; and

(f) Neurofolin has been developed to address this dietary imbalance in those individuals suffering from MDD who also suffer from an inability to adequately metabolise folate (rather than being for the *treatment* of such individuals).

2.3 The detailed scientific evidence we have provided to the TGA has also consistently supported the view that Neurofolin is to be used under medical supervision, is for dietary support, and is not marketed or presented as being a substitute for medical treatment for depression.

'Exclusive or partial feeding'

2.4 Neurofolin is specifically formulated for the dietary management of individuals by way of partial feeding. Neurofolin contains two active ingredients:

(a) L-5-Methyltetrahydrofolate calcium, an active form of the folate known to be deficient in individuals with folate metabolism disorders, common in patients suffering Major Depressive Disorder; and

(b) cyanocobalamin, to ensure adequate B12 status to make use of the supplied L-5-Methyltetrahydrofolate calcium, and to reduce the risk of making a B12 deficiency.

2.5 The other ingredients of Neurofolin are all food ingredients. Neurofolin has been specifically formulated as a 'partial feeding' product - it is not a nutritionally complete product. There is no requirement within the Food Standards Code that a FSMP provide both macronutrients and micronutrients. Neurofolin provides the required amount of 5-MTHF and Vitamin B12 as a product for 'partial feeding' to address the specific dietary requirements of target individuals.

Individuals 'who have special medically determined nutrient requirements' or 'whose capacity is limited or impaired to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients in ordinary food'

2.6 Neurofolin has been specially formulated for the dietary management of individuals 'who have special medically determined nutrient requirements'. Those individuals:

(a) have an inborn inability to metabolise folate which is medically determined (and which is common in patients suffering from MDD), and

(b) for this reason, have a 'special medically determined nutrient requirement' for folate which requires 'dietary management' (as referred to in the chapeau), in the form of L-5-MTHF.

Individuals whose 'dietary management cannot be completely achieved without the use of the food'

2.7 The detailed scientific evidence we have provided to the TGA consistently supports the view that Neurofolin has been specifically formulated for individuals whose dietary management cannot be completely achieved without the use of the food. The evidence we have provided shows that it is not sufficient to provide target individuals with regular dietary folate or other forms of vitamins, due to the markedly reduced ability of these individuals to metabolise folate.

2.8 In particular, the evidence we have provided suggests:

(a) up to 70% of MDD patients show a markedly reduced ability to convert folate to L-5-Methylfolate (L-5-MTHF), a feature not able to be remedied by intake of normal food. Therefore, this relatively common mutation can lead to a functional alteration of the metabolic processing of folate to L-5-MTHF, resulting in a dietary deficiency of L-5-MTHF in the cerebrospinal fluid (CSF);

(b) the amount of 15mg/day of L-5-MTHF included in Neurofolin is based on trials where dietary management was found to be helpful in assisting pharmacological treatment and those testing a response to L-5-MTHF; and

(c) a 15mg dose of L-5-MTHF is suitable to meet the dietary requirements of certain individuals with this metabolic imbalance, and this amount cannot be completely achieved without the use of the food.

Conclusion on FMSP

2.9 If the TGA makes a s 7 declaration that has the effect of deeming Neurofolin to be a therapeutic good then, as a matter of logic, a consistent application of the TGA's view would necessarily have an effect on the classification of a range of FSMP products, particularly those designed for metabolism disorders. This broader definitional issue, which applies across the FSMP category, should not be used to target Neurofolin.

2.10 Neurofolin is a FSMP. To substantiate Grunbiotics' consistent position that Neurofolin is specially formulated for the dietary management of patients suffering from depression to fulfil their metabolic need of key vitamins, and that it meets the definitional requirements of Standard 2.9.5, we continue to rely on all of the advice and scientific evidence previously presented to the TGA since June 2018.

2.11 We note that Neurofolin is regarded as a FSMP in several countries.

2.12 For completeness, we note that we have not had an indication from the TGA as to which aspects of this evidence - if any - the TGA takes issue with.

3. **Neurofolin is not for therapeutic use and is not represented as being for therapeutic use**

3.1 Neurofolin does not:

(a) cure or alleviate folate metabolism disorders; or

(b) modify any physiological process in an individual.

Rather, Neurofolin supplies folate in a form which is readily absorbed by individuals who would otherwise be incapable of taking, digesting, metabolising or absorbing (to use the language of the definition of a FSMP in the Code) folate from ordinary food.

3.2 Neurofolin, in the form in which it currently is sold, is also not represented as being for therapeutic use. It is represented as being a food for special medical purposes; a food which supplies folate to individuals who could not otherwise obtain folate from ordinary food. To the extent that the TGA is concerned about the use of the word 'depression' in relation to Neurofolin, we have suggested several alternative indications.

3.3 Grunbiotics has provided the TGA with scientific and legal evidence to support the position that Neurofolin is not for therapeutic use. In the absence of any evidence to the contrary, we submit it is not arguable that the product is 'likely' to be taken to be for therapeutic use.

3.4 In accordance with the advice of the many independent experts engaged by Grunbiotics, we believe Neurofolin has always been in compliance with Standard 2.9.5 in terms of its classification and its presentation and claims.

4. **No evidence that Neurofolin is taken to be for therapeutic use**

4.1 Grunbiotics commissioned an independent consumer research report in August 2018. In the survey more than 200 consumers were asked whether they thought a prescription was needed for Neurofolin. A very small minority (approx. 5%) of consumers saw Neurofolin as potentially a therapeutic good (requiring a prescription). The vast majority did not hold such a view.

4.2 Grunbiotics has had no anecdotal feedback from pharmacists or other health professionals that Neurofolin is taken by consumers to be for therapeutic use. We do not believe that there is any evidence which justifies such a conclusion and nor have we been provided with any evidence or other material which would support it.

4.3 Anecdotal testing undertaken using the newly amended product, to identify if consumers potentially see Neurofolin as a therapeutic good, indicate no consumers see Neurofolin as being for therapeutic use.

4.4 Grunbiotics believes (on the basis of the previous consumer research we have undertaken which tested similar issues) that if consumer research were to be commissioned, the outcome of that research would be that consumers do not take Neurofolin to be for therapeutic use.

5. **The draft s 7 declaration is unreasonably broad**

5.1 We note that the effect of the declaration is that a folate-containing FSMP will be deemed to be a therapeutic good if it is likely to be taken for therapeutic use, which is expressed to include:

(a) curing or alleviating an inborn error of metabolism; and

(b) preventing, curing or alleviating folate deficiency.

5.2 The inclusion of these two indications makes the draft s 7 declaration unreasonably broad in effect for three reasons. First, there does not appear to be any principled reason why an individual who has an inborn error of metabolism or a folate deficiency should be deprived the benefit of a FSMP as opposed to an individual who has any other kind of metabolism disorder.

5.3 Secondly, the declaration creates disharmony between the Therapeutic Goods Act and the FSANZ Code. Notwithstanding the provisions of s 7(1A) of the Therapeutic Goods Act, the FSANZ Code the and the Therapeutic Goods Act should be read together on the basis that their provisions are intended to give effect to harmonious goals. The declaration as drafted defeats any sense of harmony between these two instruments.

5.4 This is because the breadth of the declaration as drafted uses the Therapeutic Goods Act to remove any scope for the work which Standard 2.9.5 was intended to perform. Standard 2.9.5-10(1)(c) explicitly contemplates that FSMPs are intended to have a 'medical purpose'. Having regard to the interaction between the concept of 'therapeutic use' in the Therapeutic Goods Act and Standard 2.9.5, there must be a distinction between FSMPs (which are nutritional supports intended to address inborn errors of metabolism) and goods which are intended for therapeutic use. The declaration as drafted -impermissibly, in our view - conflates these two distinct statutory concepts.

5.5 Thirdly, the declaration as drafted would deprive consumers of a FSMP which is regularly recommended by pharmacists and medical practitioners as part of clinical good practice. The *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders* recommends folate, including L-Methylfolate, for depression, stating that it may 'assist depressive symptoms as adjunct to prescription medication.' We have letters of support from psychiatrists and pharmacists to the effect that Neurofolin is a valuable component in the full range of clinical tools to assist patients with depression. We are concerned that the actions of the TGA would deprive a large number of Australians of the benefits of a product that is:

(a) safe;

(b) recommended in the RANZCP guidelines; and

(c) widely used as part of clinical good practice in Australia.

6. **No health and safety issue**

6.1 We are not aware of any health or safety issue with Neurofolin. Nor are we aware that anyone has raised any health or safety concern with the TGA in relation to Neurofolin.

6.2 It is relevant in deciding whether to make a s 7 declaration for the delegate to consider that:

- Neurofolin is recommended as part of clinical psychiatric practice and it can be expected that is widely recommended by psychiatrists;
- we have been provided with a letter from Professor Ashley Bush (Director, Melbourne Dementia Research Centre) dated 18 July 2019 in which Professor Bush stated that:

  > *L-methylfolate has been shown in clinical trials to be safe and is effective in ameliorating the impairments in folate uptake and retention …*;

- following the TGA requiring Grunbiotics to undertake a Class III recall in respect of Neurofolin, the TGA recall representative confirmed that there is no health or safety concern in relation to Neurofolin;
- Grunbiotics has not received any report of adverse events associated with Neurofolin and nor are we otherwise aware of any; and
- the TGA's own Explanatory Statement Therapeutic Goods (Listing) Notice 2015 in relation to levomefolate calcium (L-5-methylfolate) which was made when L-5-methylfolate was added to the list of permissible ingredients states:

  > *Single-dose, repeat-dose and reproductive toxicity tests in animal models have shown no treatment-related effects at the highest doses used. Additionally, there was no evidence of genotoxicity in a battery of ICH-compliant in vivo and in vitro tests. No adverse effects of Levomefolate calcium supplementation up to 17 mg per day were observed in numerous parallel, randomised, placebo-controlled human clinical trials.*

Yours Sincerely

[redacted]

Rebecca Emblin
Director