From: EDLINGTON, Mandy
To: COOK, Jane
Cc: FRANCIS, Jenny; s22
Subject: Additional attachment to minute regarding proposed declaration regarding folate [SEC=OFFICIAL, ACCESS=Legal-Privilege]
Date: Wednesday, 30 October 2019 3:15:38 PM
Attachments: image002.png
Part of Attachment E - email of 15 October 2019.pdf

Dear Jane

Further to my emails in relation to the proposed declaration, please find ***attached*** an additional document that should have been included in **Attachment E** of the hard-copy package provided to you on Friday afternoon, but appeared to be omitted from the electronic compilation.

Kind regards

Mandy Edlington
Practice Group Leader | Legal Advisings and Legislation Sections

Regulatory Legal Services Branch | Health Products Regulation Group
Australian Government Department of Health
T: s22 | E: s22 @health.gov.au
PO Box 100 Woden ACT 2606 Australia | Location: Symonston GD35

Please note that I leave work at 3.45pm on Wednesdays and Thursdays.

s42

s42

s42

GEDDES, Jane

From: RC
Sent: Tuesday, 15 October 2019 4:40 PM
To: s22
Subject: RE: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]
Attachments: A Controlled Trial of Homocysteine Lowering and Cognitive Performance.pdf

Dear s22

Further to my email below, we wish to refer you to a supplementary article (attached) that Dr Ken Harvey has forwarded to the TGA yesterday.

We do not envisage that the article will necessarily require comment but wish to bring the article to your attention, as a matter of courtesy, because it contributes to the general body of scientific literature regarding the basis on which folate may be taken to be for therapeutic use.

As noted in previous correspondence, if you do wish to comment, we invite you to do so by Friday 18 October.

Regards,

s22
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Phone: s22
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: RC <RC@health.gov.au>
Sent: Wednesday, 9 October 2019 4:30 PM
To: s22
Subject: RE: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]

Dear s22

Further to my email below, for your information we note that there are several sections in the 2 pieces of information referred to below (and which we emailed to you on Friday last) specifically pertaining to folate substances for therapeutic uses, in particular:

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders

- Table 17 entry in relation to Folate and references cited (Taylor et al. (2004), Nielsen et al. (2015))
- Page 46

Firth et al 2019

- The ***Results*** section relating to Folate-based supplements (pp 311-314)
- ***Table 2*** in relation to key findings and indicated usage of folate-based supplements / methylfolate as adjunctive treatment in MDD and Schizophrenia
- ***Discussion*** relating to adjunctive treatment with folate-based supplements (page 321)

Consideration of whether to make the proposed declaration under s 7 of the *Therapeutic Goods Act 1989* requires the delegate to consider whether he or she is satisfied whether the class of goods specified in column 2 of the table in Schedule 2 of the proposed declaration are therapeutic goods when used, advertised or presented for supply for therapeutic use, or in a way that is likely to be taken to be for therapeutic use where that use can be taken to relate to a folate substance mentioned in paragraph (a) in column 2 of the table in Schedule 2.

Regards,

s22 [redacted]
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Phone: s22 [redacted]
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: RC
Sent: Wednesday, 9 October 2019 12:47 PM
To: s22 [redacted]
Subject: RE: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]

Dear s22 [redacted]

Please disregard the previous email. The extension for comments has been amended to Friday 18 October 2019.

Regards,

s22 [redacted]
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Phone: s22
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: RC <RC@health.gov.au>
Sent: Wednesday, 9 October 2019 9:37 AM
To: s22
Subject: RE: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]

Dear s22

As the period for comment included a public holiday in 3 states and territories, we are extending the date to receive your comments to Monday 14 October 2019.

Regards,

s22
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Phone s22
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: RC
Sent: Friday, 4 October 2019 4:13 PM
To: s22
Subject: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]

Dear s22

Thank you for your submission to the TGA's public consultation process on the proposed clarification that goods are therapeutic goods – goods containing folate substances in certain circumstances.

We invite you to make comments to us on the *attached* documents (as follows) we have received during the consultation process which may be relevant to the delegate's consideration of whether to make a declaration under s 7 of the *Therapeutic Goods Act 1989*:

- Complaint received from Dr Ken Harvey, Medreach Pty Ltd, Dr Harvey's FOI request to the Department of Health (the TGA) and document disclosed to Dr Harvey to comply with the request
- Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (2015)
- Firth et al – *The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials* World Psychiatry 2019; 18:308-324

You are requested to please give us your comments by close of business on Friday 11 October 2019.

Regards,

s22
[redacted]
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Phone: s22
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

To: Jane Cook, FAS Medicines Regulation

SUBJECT **PROPOSED ORDER DECLARING THAT CERTAIN GOODS CONTAINING FOLATE SUBSTANCES ARE THERAPEUTIC GOODS**

Purpose

To seek your consideration and approval, as delegate of the Secretary under section 7 of the *Therapeutic Goods Act 1989* ("the Act"), regarding the making of the *Therapeutic Goods Amendment (Declared Goods) Order 2019* ("the Amendment Order") at **Attachment A.1.**

Timing

For consideration at your earliest convenience, noting public consultation and further processes inviting comment have been completed.

Issues/Sensitivities

The purpose of the Amendment Order is to clarify that the goods specified in Schedule 1 to the Amendment Order ("the relevant goods") are therapeutic goods, and so subject to regulation under the Act (rather than the separate regulatory scheme for foods).

Public consultation closed on 18 September 2019 in respect of a proposed declaration in largely similar terms. The consultation paper is at **Attachment B**. 25 submissions were received from a range of respondents and can be found at **Attachment C**.

While one submission supported the principle of the proposed clarification, the majority of submissions objected to the proposal on the basis of the following:

- financial and other impacts on a particular entity (and its investors and staff); and
- potential loss of access by users of relevant goods and consequent hardship;

Further, it was submitted there was no need for the declaration or, alternatively, the scope of the declaration should be narrowed – this included the view that the relevant goods were currently being appropriately regulated by the *Australia New Zealand Food Standards Code* – Standard 2.9.5 – Food for special medical purposes (at **Attachment D)**.

The TGA provided respondents with a further opportunity to comment on material before the TGA, including information provided by Dr Ken Harvey. See **Attachment E** for a copy of this material. The 17 supplementary comments received can be found at **Attachment F**. The general tenor of the comments was that the extra material did not change the respondents' views. Further, there was criticism of Dr Harvey's views; and a general view that the scientific article titled "A Controlled Trial of Homocysteine Lowering and Cognitive Performance" (at **Attachment E**) was not relevant.

The explanatory statement for the Amendment Order (at **Attachment A.2**) addresses the concerns raised during the consultation process.

We also draw your attention to a selection of articles at **Attachment G** concerning the general body of scientific literature in the public domain regarding the use of folate substances (noting this is not intended to be exhaustive).

Consultation

Public consultation was conducted and further invitations to comment were provided as mentioned above.

All relevant areas of the HPRG were consulted in the preparation of the Amendment Order, including the Complementary and OTC Medicines Branch, the Regulatory Education and Compliance Branch, and the Regulatory Legal Services Branch.

Recommendation

Should you decide that the relevant goods (when used, advertised, or presented for supply in a particular way) are therapeutic goods and it is appropriate to make the order, it is recommended that you:

1) sign the Amendment Order at **Attachment A.1**; and
2) approve the accompanying explanatory statement at **Attachment A.2**.

Attachment A.1 Signed / Not Signed / Please Discuss

Attachment A.2 Approved / Not Approved / Please Discuss

Jane Cook
FAS, Medicines Regulation
/ / 2019

Copy to:

Attachments:

A.1 *Therapeutic Goods Amendment (Declared Goods) Order 2019*
A.2 Explanatory Statement for the *Therapeutic Goods Amendment (Declared Goods) Order 2019*
B. Public consultation paper
C. Submissions made on consultation
D. Food Standard 2.9.5 – Food for special medical purposes
E. Invitations to comment on supplementary material
F. Comments made on supplementary material
G. Non-exhaustive selection of scientific articles

Contact officers:	Adam Cook and Mandy Edlington
Phone:	s22 [redacted]
TRIM ref:	D19-6230899
Cleared by:	Cheryl McCrae

Therapeutic Goods Amendment (Declared Goods) Order 2019

I, Jane Cook, as delegate of the Secretary of the Department of Health, make the following order.

Dated October 2019

Dr Jane Cook
First Assistant Secretary
Medicines Regulation Division
Health Products Regulation Group
Department of Health

Contents

1 Name

This instrument is the *Therapeutic Goods Amendment (Declared Goods) Order 2019*.

2 Commencement

(1) Each provision of this instrument specified in column 1 of the table commences, or is taken to have commenced, in accordance with column 2 of the table. Any other statement in column 2 has effect according to its terms.

Commencement information		
Column 1	**Column 2**	**Column 3**
Provisions	**Commencement**	**Date/Details**
1. The whole of this instrument	The day after this instrument is registered.	

Note: This table relates only to the provisions of this instrument as originally made. It will not be amended to deal with any later amendments of this instrument.

(2) Any information in column 3 of the table is not part of this instrument. Information may be inserted in this column, or information in it may be edited, in any published version of this instrument.

3 Authority

This instrument is made under section 7 of the *Therapeutic Goods Act 1989*.

4 Schedules

Each instrument that is specified in a Schedule to this instrument is amended or repealed as set out in the applicable items in the Schedule concerned, and any other item in a Schedule to this instrument has effect according to its terms.

Schedule 1—Amendments

Therapeutic Goods (Declared Goods) Order 2019

1 Part 2 of Schedule 1 (at the end of the table)

Add:

3	goods that: (a) contain one or more of the following folate substances: (i) folic acid; or (ii) folinic acid; or (iii) levomefolic acid; or (iv) any other form of folate that may be characterised as an active principle, precursor, derivative, salt, ester, ether or stereoisomer; and (b) are represented as being food for special medical purposes, or being for dietary management of a disease, disorder or medical condition; whether or not the recommended single dose of the goods contains sufficient macronutrients to feed, either exclusively or partially, the person for whom the dose is intended	when used, advertised, or presented for supply: (a) for therapeutic use; or (b) in a way that is likely to be taken to be for therapeutic use; including, but not limited to, one or more of the following therapeutic uses: (c) preventing, curing or alleviating depression; (d) curing or alleviating an inborn error of folate metabolism; (e) preventing, curing or alleviating folate deficiency; and that therapeutic use can be taken to relate to a substance mentioned in paragraph (a) in column 2 of this item

EXPLANATORY STATEMENT

Therapeutic Goods Act 1989

Therapeutic Goods Amendment (Declared Goods) Order 2019

The *Therapeutic Goods Act 1989* ("the Act") provides for the establishment and maintenance of a national system of controls for the quality, safety, efficacy and timely availability of therapeutic goods that are used in, or exported from, Australia. The Act is administered by the Therapeutic Goods Administration ("the TGA") within the Australian Government Department of Health.

Subsection 3(1) of the Act relevantly provides that '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. That definition relevantly excludes goods (other than goods declared to be therapeutic goods under an order in force under section 7) for which there is a standard within the meaning of subsection 4(1) of the *Food Standards Australia New Zealand Act 1991* (paragraph (e) of the definition of therapeutic goods refers).

Subsection 7(1) of the Act confers on the Secretary of the Department a power to declare, by order published in the *Gazette* or on the Department's website, that particular goods or classes of goods, or those goods when used, advertised, or presented for supply in a particular way, are or are not therapeutic goods for the purposes of the Act. In making a declaration that goods are or are not therapeutic goods, the Secretary must be satisfied that the goods are or are not in fact therapeutic goods as defined in the Act. In short, subsection 7(1) provides a mechanism for clarifying whether particular goods or classes of goods are or are not therapeutic goods, and therefore whether or not those goods are subject to the regulatory scheme established by the Act.

In determining whether particular goods or classes of goods, or those goods when used, advertised, or presented for supply in a particular way, are therapeutic goods, subsection 7(1A) of the Act provides that the Secretary must disregard paragraphs (e) and (f) of the definition of 'therapeutic goods' in subsection 3(1). As mentioned above, paragraph (e) refers to goods for which there is a standard under subsection 4(1) of the *Food Standards Australia New Zealand Act 1991*, with the effect that those goods are excluded from the definition of 'therapeutic goods'. Similarly, paragraph (f) refers to goods which have a tradition of use as foods for humans in the form in which they are presented, with the effect of excluding goods which have a tradition of use as foods from the definition of therapeutic goods. Accordingly, subsection 7(1A) has the purpose and effect of ensuring that an order declaring goods to be therapeutic goods under section 7 of the Act may bring certain goods within the scope of the Act, notwithstanding any food standard that may otherwise apply to those goods, or whether those goods have a tradition of use as foods.

The *Therapeutic Goods (Declared Goods) Order 2019* ("the Principal Order") is made under section 7 of the Act. The Principal Order declares particular goods or classes of goods, or those goods when used, advertised, or presented for supply in a particular way, to be therapeutic goods, or not to be therapeutic goods, for the purposes of the Act.

The *Therapeutic Goods Amendment (Declared Goods) Order 2019* ("the Amendment Order") is made under section 7 of the Act, read together with subsection 33(3) of the *Acts Interpretation Act 1901*. The Amendment Order amends the Principal Order by declaring certain goods containing folate substances ("the relevant goods") to be therapeutic goods when used, advertised, or presented for supply for therapeutic use, or in a way that is likely to be taken to be for therapeutic use.

The Amendment Order clarifies that the relevant goods are indeed therapeutic goods as defined by the Act and therefore subject to the national system of controls established by the Act. This measure addresses uncertainty about the proper characterisation of the relevant goods as a consequence of the *Australia New Zealand Food Standards Code* – Standard 2.9.5 – Food for special medical purposes

("Food Standard 2.9.5"). The effect of the Amendment Order is to confirm that the relevant goods are therapeutic goods for the purposes of the Act, irrespective of any view regarding the application of Food Standard 2.9.5 to the relevant goods prior to the making of this Amendment Order.

The power to declare in subsection 7(1) is a discretionary power to be exercised having regard to the objects of the Act (section 4 of the Act refers). In this case, the exercise of that power is particularly useful in resolving uncertainty or differences of opinion regarding the proper characterisation of certain goods at the food medicine interface. The power to declare therefore provides an appropriate mechanism to address regulatory uncertainty by enabling the Secretary to declare particular goods to be therapeutic goods, irrespective of whether or not those goods are goods for which there is a food standard.

Background

An understanding of the regulatory frameworks for therapeutic goods and foods, as follows, necessarily informs the background for making the Amendment Order.

Regulation of therapeutic goods in Australia

The regulation of therapeutic goods in Australia is the principal responsibility of the Australian Government. The purpose of the Act is to provide for the establishment and maintenance of a national system of controls relating to the quality, safety, efficiency and timely availability of therapeutic goods. The controls relate to a range of measures that Parliament has considered appropriate in regulating therapeutic goods, including requirements relating to the lawful supply and advertisement of medicines.

Therapeutic goods are relevantly defined in subsection 3(1) of the Act to mean 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. The definition does not include goods that come within paragraphs (e) and (f) of the definition, unless those goods are declared to be therapeutic goods under an order in force under section 7 of the Act.

In making an order under section 7 of the Act, subsection 7(1A) provides that the Secretary must disregard paragraphs (e) and (f) of the definition in deciding whether particular goods or classes of goods are therapeutic goods, either generally or when used, advertised or presented for supply in a particular way.

Therapeutic use is defined in subsection 3(1) of the Act, amongst other things, to include use in or in connection with preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons, or use in or in connection with influencing, inhibiting or modifying a physiological process.

Regulation of foods in Australia

The regulation of food in Australia is a joint responsibility of the Commonwealth and the states and territories. Food Standards Australia New Zealand ("FSANZ") is responsible for the Australia New Zealand Food Standards Code ("the Food Standards Code"), a set of national standards for food under the *Food Standards Australia New Zealand Act 1991*.

State and territory government food authorities and local councils enforce the Code through their respective legislation, and deal with complaints regarding food and investigate food safety issues. The Department of Agriculture enforces food laws at Australia's borders in relation to imported food.

Foods are permitted to be supplied to consumers without prior regulatory approval by state and territory food authorities. Therefore, goods may be brought to market as foods without prior regulatory assessment as to whether those goods are indeed foods or therapeutic goods under law.

Goods at the interface of the food and medicines frameworks

Goods at the interface of the food and medicines frameworks give rise to uncertainty, or potential uncertainty, as to which of the regulatory frameworks applies in relation to those goods. This stems, in part, from the interplay between the definitions of *therapeutic goods* and *therapeutic use* in the Act; and the presentation and health claims made in relation to some foods, for which permission may or may not be provided in the relevant food standards.

Goods that are, or are likely to be taken to be, for use in preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons, or modifying a physiological process, are therapeutic goods, unless—in the absence of a relevant order under section 7 of the Act—there is an existing food standard applying in relation to those goods.

Food Standard 2.9.5 – Foods for special medical purposes

Food Standard 2.9.5 applies to foods for special medical purposes. A food for special medical purposes ("FSMP") is defined to mean a food that, amongst other requirements, is specially formulated for the dietary management of individuals, by way of exclusive or partial feeding, in relation to whom there are 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 whose dietary management cannot be completely achieved without the use of the food. Other requirements include that the food is represented as being a food for special medical purposes, or for the dietary management of a disease, disorder or medical condition.

Food Standard 2.9.5 distinguishes between representations related to food for special medical purposes or dietary management, which are permitted for goods in relation to which the standard applies, from those related to therapeutic use, which is not permitted in relation to foods for special medical purposes. This is consistent with there being separate regulatory regimes in Australia relating to foods and therapeutic goods. In particular, a claim in relation to an FSMP must not refer to the prevention, diagnosis, cure or alleviation of a disease, disorder or condition, or the modification of a physiological process. Nor must a claim compare the food with a good that is represented in any way to be for therapeutic use, or likely to be taken to be for therapeutic use, whether because of the way in which the good is presented or for any other reason (section 2.9.5–4 of Food Standard 2.9.5 refers).

Characterisation of foods for special medical purposes

Some goods that are purported to be FSMPs are marketed and supplied to consumers in circumstances where those goods are represented as being, or likely to be taken to be, for therapeutic use. This situation may arise due to a misunderstanding regarding the interpretation of the definition of an FSMP in Food Standard 2.9.5 and the definition of therapeutic goods in the Act. Some products are mistaken for foods because it is assumed that Food Standard 2.9.5 applies. In any case, the application of Food Standard 2.9.5 is irrelevant for the purposes of making an order under section 7 of the Act.

Considerations

In exercising the power under subsection 7(1) to declare certain goods, the Secretary must be satisfied that the goods are therapeutic goods within the meaning of the Act. Whether or not there is a food standard applying in relation to the goods is irrelevant to the exercise of the power (subsection 7(1A) refers). Ultimately, it is a matter for the Secretary or her delegate to determine whether such goods should be declared to be therapeutic goods under subsection 7(1) because those goods are, in the Secretary's reasonable opinion, therapeutic goods within the meaning of the Act.

In determining whether goods are therapeutic goods, the Secretary must be satisfied that the definition for 'therapeutic goods' in subsection 3(1) applies. Therapeutic goods are defined with reference to therapeutic use. Most relevantly, therapeutic goods are 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.

For present purposes, the principal aspect of the definition for therapeutic use is use in or in connection with preventing, diagnosing, curing or *alleviating* a disease, *ailment*, defect or injury in persons (emphasis added) (paragraph (a) of the definition for 'therapeutic use' refers). Accordingly, the assessment as to the proper characterisation of the relevant goods is predicated on a reasonable assessment of whether or not the goods 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, specifically the alleviation of an ailment.

In the alternative, the assessment therapeutic use may also extend to whether or not the relevant goods 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 modify a physiological process in persons (paragraph (b) of the definition for 'therapeutic use' refers).

In light of the above, the following matters were considered and necessarily found in making the Amendment Order.

Depression is an ailment in persons

The ordinary meaning of depression, as defined in the Macquarie Dictionary, is 'a mental disorder characterised by unresponsiveness to stimuli, self-depreciation, delusions of inadequacy and hopelessness'. Depression is characterised as a disorder that 'specifically affect[s] the individual's capacity to function.'[1] As such, it is appropriate to conclude that depression is an ailment in persons.

Folate deficiency is an ailment in persons

Folate substances encompass the substance folic acid and its derivatives with similar biological activity. These substances are metabolised in the body to derivatives that are essential co-factors for enzymes involved in nucleic acid (DNA and RNA) synthesis, and are substrates in amino acid synthesis and metabolism, processes that are essential for human life. Folate substances are particularly important for developmental phases and physiological processes that involve rapid cell replication, such as foetal and red blood cell development. Therefore, deficiency in folate is associated with and mechanistically linked to a variety of ailments and defects in persons. Folate deficiency can result from an inborn error of metabolism, or a deficiency for another reason, such as insufficient dietary intake. Folate deficiency is considered to be an ailment in persons.

There is an association and plausible causal relationship between folate deficiency and depression

The level of folate substances in red blood cells, serum and/or cerebrospinal fluid has been found to be significantly altered in a substantial yet variable proportion of patients with major depressive disorder ("MDD") compared to control individuals.[2,3] Folate plays a role in processes that are linked to the synthesis of neurotransmitters, the dysregulation of which is linked to depression. This means that there is a biologically plausible molecular mechanism by which folate deficiency in persons

[1] *Diagnostic and Statistical Manual of Mental Disorders DSM-5* (American Psychiatric Association, 5th ed, 2013).
[2] Simon Gilbody, Tracy Lightfoot, Trevor Sheldon, 'Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity' (2007) 61 *Journal of Epidemiology and Community Health* 631.
[3] Ansley Bender, Kelsey Hagan, Neal Kingston, 'The association of folate and depression: A meta-analysis' (2017) 95 *Journal of Psychiatric Research* 9.

(evidenced by reduced levels of folate substances in cells, serum and/or cerebrospinal fluid) dysregulates cellular processes in the central nervous system, thereby causing or exacerbating the incidence or severity of mental illnesses, including depression.[4,5]

Folate deficiency in persons can result from an inborn error of folate metabolism

The methylenetetrahydrofolate reductase ("MTHFR") gene encodes the cognate protein that is involved in the *in vivo* metabolism of dietary folate. In some persons, the MTHFR gene is mutated at a single base pair and those persons are therefore said to carry an MTHFR C677T polymorphism, which impairs MTHFR activity. It follows that persons, who are considered to have a genetic (inborn) error of folate metabolism, have a defect in normal folate metabolism, which can lead to a deficiency in folate substances.

There is an association between an inborn error of folate metabolism due to the MTHFR C677T polymorphism and depression

It has been reported in several meta-analyses that individuals with depression are more likely to carry the MTHFR C677T polymorphism than those without.[6] It is reasonable to conclude that there is an association between an inborn error of folate metabolism as a consequence of the MTHFR C677T polymorphism and depression.

There is a plausible causal relationship between an inborn error of folate metabolism, depression, and other ailments or defects in persons

An inborn error of folate metabolism can lead to folate deficiency in persons, which in turn can cause ailments or defects in persons such as abnormal foetal development or depression for the reasons stated above. As such, the association between the MTHFR C677T polymorphism and depression suggests that folate deficiency secondary to the inborn error of folate metabolism is involved in the pathogenesis of depression.[2] The plausible causal relationship between an inborn error of folate metabolism and depression gives rise to the possibility that consumption of folate substances may alleviate depression in persons with folate deficiency.

Conclusions

Noting the above, it is appropriate that the relevant goods are characterised as therapeutic goods for the following reasons.

The relationship between an inborn error of folate metabolism and folate deficiency, together with the plausible causal relationship between folate deficiency and depression, means that folate is or is likely to be taken to be for therapeutic use in or in connection with preventing, curing or alleviating the ailment of folate deficiency or depression, or alternatively modifying a physiological process.

The consumption of goods containing folate can increase folate levels in persons, meaning that those goods may be used in or in connection with preventing, curing or alleviating the ailment of folate deficiency or curing or alleviating an inborn error folate metabolism; and such use is therapeutic use within the meaning of the Act.

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[4] Marshal Folstein et al, 'The Homocysteine Hypothesis of Depression' (2007) 164(6) *American Journal of Psychiatry* 861.
[5] Alan L Miller, 'The Methylation, Neurotransmitter, and Antioxidant Connections Between Folate and Depression' (2008) 13(3) *Alternative Medicine Review* 216.
[6] Vandana Rai, 'Association of C677T polymorphism (rs1801133) in MTHFR gene with depression' (2017) 63(6) *Cellular and Molecular Biology* 60.

Folate substances are likely to be taken to be for use in or in connection with alleviating the ailment of depression and such use is therapeutic use within the meaning of the Act. A review of meta-analyses of clinical trials in persons concludes that the administration of folate substances is beneficial in the treatment of depression[7].

Whether or not such goods may be characterised as FSMPs within the meaning of Food Standard 2.9.5 (including because the relevant goods are represented as being for the dietary management of a disease, disorder or medical condition) is irrelevant to the exercise of the power to declare the relevant goods to be therapeutic goods under section 7 of the Act. In fact, the effect of subsection 7(1A) of the Act expressly obliges the Secretary to disregard whether or not a food standard applies in relation to the goods.

Whether a recommended single dose of the goods contains sufficient macronutrients to feed, either exclusively or partially, the person for whom the dose is intended does not affect the characterisation of whether or not the relevant goods are therapeutic goods.

The fact that the relevant goods contain only folate substances that are found in food (within the ordinary meaning of the word), or that are ordinarily obtained from food, and restore levels of folate that are required for normal function, does not preclude the Secretary from declaring those goods to be therapeutic goods when used, advertised or presented for supply for therapeutic use or in a particular way that is likely to be taken to be for therapeutic use.

The power to declare goods to be therapeutic goods does not require an assessment as to whether or not those goods pose an unacceptable risk to human health if regulated as foods. However, the effect of the Amendment Order necessarily ensures that the relevant goods will be regulated under the Act as therapeutic goods – principally medicines, that may be required to be registered or listed in accordance with the Act and instruments made thereunder, having regard to the relevant risk. This ultimately depends on the amount of folate in the goods and the associated therapeutic claims.

The fact that such goods may be used as adjunct therapies for conditions such as depression (working in conjunction with prescription medicines), and containing substances ordinarily consumed from diet, does not mean that these goods are not themselves medicines. Indeed, it is appropriate in the circumstances that the relevant goods are subject to the national system of controls relating to therapeutic goods which may be described as complementary medicines.

Consultation

The TGA undertook public consultation in September 2019 regarding the proposal to make an order under subsection 7(1) of the Act to declare a particular class of goods containing folate substances to be therapeutic goods. As part of the public consultation, the TGA published the proposed declaration, which is in largely similar terms to the Amendment Order. Twenty-five submissions were received from a range of respondents including investors, consumers, academics, health professionals, health-related organisations and persons associated with corporate entities that may be affected by the proposed declaration, including manufacturers and suppliers.

Following the public consultation, the TGA provided further relevant information in October 2019 to the persons who had made submissions to the public consultation (being information before the TGA, including information provided by other parties) and invited supplementary comment.

A number of submissions objected to the terms of the proposed declaration on the basis of the anticipated financial and other impacts that the proposed declaration would have on a particular entity, including its investors and staff. That entity is presently supplying goods that would appear to fall

[7] Joesph Firth et al, 'The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials' (2019) 18 *World Psychiatry* 308.

within the terms of the declaration; and the impacts would therefore include the practical requirements for registering or listing the goods on the Australian Register of Therapeutic Goods ("the Register").

A related issue raised by some respondents was the potential loss of access by consumers of the affected goods, which have been manufactured and supplied as if those goods were not subject to the therapeutic goods framework but, following the making of the declaration, would clearly fall to be so regulated. These respondents made submissions regarding the consequent hardship on consumers if the proposed declaration were to be made. A number of respondents were concerned that relevant schemes under the Act relating to alternative access (that is, the Authorised Prescriber Scheme and the Special Access Scheme) would not be effective.

The relevant goods affected by the declaration may continue to be supplied to consumers under the alternative access schemes until such time as those goods are registered or listed on the Register. The alternative access schemes are means by which the impact on affected entities currently supplying goods within the terms of the declaration and consumers using those goods may be managed. The schemes involve health practitioners facilitating access to goods which are not presently approved for general marketing in Australia. This is reasonable in the circumstances given that the goods 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.

Another issue raised in submissions received in response to the public consultation was that the declaration would preclude dietary management of patients with inborn errors of metabolism. That is, that dietary requirements in this regard would no longer be able to be addressed by FSMPs. However, the possibility of dietary management, including of a disease, disorder or medical condition, would remain if goods containing folate substances are not used, advertised or presented for supply in any way that is likely to be taken to be for therapeutic use. This was recognised in one of the submissions. For example, in individuals whose capacity to take folate substances from ordinary food is impaired due to a disorder that precludes the consumption of foods containing normal dietary sources of folate, then the dietary management of those individuals may require use of goods containing folate substances (folate being an essential vitamin in persons).

A number of submissions questioned the need for, and the scope of, the declaration. The view of some respondents was that Food Standard 2.9.5 deals with goods that are within the scope of the declaration adequately. This view appeared to be on the basis that goods containing only substances ordinarily consumed from the diet (which is the case for some folate substances) are appropriately characterised FSMPs. Further, a number of respondents considered there was no indication that folate should be considered a therapeutic treatment, or no evidence of safety or efficacy issues with products that may be affected by the declaration. These respondents also indicated that, if the declaration was to be made, it could be narrowed or made clearer.

It is evident from the consultation that there are differing views as to whether affected products are to be seen as FSMPs or therapeutic goods. The evidence for the association between folate and therapeutic use has been referred to above. While affected goods may simply be an adjunct therapy for conditions such as depression (working in conjunction with any prescription medicines), and contain substances ordinarily consumed from the diet, as mentioned above, this does not mean those goods are not themselves medicines. Indeed, goods captured by the declaration would be regulated as complementary medicines, whether or not those goods may fall to be registered or listed on the Register. To narrow the scope of the declaration would detract from the purpose of ensuring relevant goods are regulated by the most appropriate regulatory scheme. It is appropriate that the declaration therefore provide clarification at the interface of the food and medicine frameworks in relation to these goods.

There was also a specific concern raised in one submission that the general reference to 'inborn error of metabolism' in paragraph (d) of column 3 of the proposed declaration would be interpreted too broadly, and should therefore be specified with reference to folate metabolism. This submission

resulted in an amendment being made to the proposed declaration (now reflected in this Amendment Order) duly referencing folate metabolism.

Another submission, although raising some issues about the scope of the proposed declaration discussed above, supported the clarifying intent that when goods claiming to be food for special medical purposes, are presented for therapeutic use, those goods should be regulated as therapeutic goods with the appropriate quality, safety and efficacy controls.

On balance, it is appropriate that the power under subsection 7(1) of the Act is exercised to provide clarity and certainty regarding the regulation of goods within the terms of the Amendment Order. These goods, when represented in any way to be, or 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, are appropriately characterised as therapeutic goods, and should therefore be subject to the national system of controls under the Act for therapeutic goods.

Details of the Amendment Order are set out in **Attachment A.**

The Amendment Order is compatible with human rights and freedoms recognised or declared under section 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*. A full statement of compatibility is set out in **Attachment B.**

The Amendment Order is a disallowable legislative instrument for the purposes of the *Legislation Act 2003* ("Legislation Act") and commences on the day after it is registered on the Federal Register of Legislation. Under subsection 56(1) of the Legislation Act, the requirement for the Amendment Order to be published in the *Gazette* under section 7 of the Act, is satisfied by registration of the Amendment Order as a legislative instrument.

Attachment A

Details of the *Therapeutic Goods Amendment (Declared Goods) Order 2019*

Section 1 – Name

This section provides that the name of the instrument is the *Therapeutic Goods Amendment (Declared Goods) Order 2019* ("the Amendment Order").

Section 2 – Commencement

This section provides that the Amendment Order commences on the day after it is registered on the Federal Register of Legislation.

Section 3 – Authority

This section provides that the legislative authority for making the Amendment Order is section 7 of the *Therapeutic Goods Act 1989* ("the Act").

Subsection 33(3) of the *Acts Interpretation Act 1901* relevantly provides that, where an Act confers a power to make, grant or issue any instrument of a legislative or administrative character, the power shall be construed as including a power exercisable in the like manner and subject to the like conditions (if any) to repeal, rescind, revoke, amend, or vary any such instrument. This instrument is made in accordance with that provision.

Section 4 – Schedules

This section provides that each instrument that is specified in a Schedule to the Amendment Order is amended or repealed as set out in the applicable items in the Schedule concerned, and that any other item in a Schedule to the instrument has effect according to its terms.

Schedule 1—Amendments

This Schedule amends the *Therapeutic Goods (Declared Goods) Order 2019* ("the Principal Order"). Item 1 of this Schedule inserts a new item 1A into the table in Part 2 of Schedule 1 to the Principal Order. The effect of this amendment is to declare certain goods containing folate substances that are represented as being food for special medical purposes, or being for the dietary management of a disease, disorder or medical condition to be therapeutic goods when used, advertised, or presented for supply for therapeutic use.

Attachment B

Statement of Compatibility with Human Rights

Prepared in accordance with Part 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*

Therapeutic Goods Amendment (Declared Goods) Order 2019

This disallowable legislative instrument is compatible with the human rights and freedoms recognised or declared in the international instruments listed in section 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*.

Overview of legislative instrument

The *Therapeutic Goods Amendment (Declared Goods) Order 2019* ("the instrument") is made under section 7 of the *Therapeutic Goods Act 1989* ("the Act").

Subsection 7(1) of the Act confers on the Secretary of the Department a power to declare, by order published in the *Gazette* or on the Department's website, that particular goods or classes of goods, or those goods when used, advertised, or presented for supply in a particular way, are or are not therapeutic goods for the purposes of the Act. In making a declaration that goods are or are not therapeutic goods, the Secretary must be satisfied that the goods are or are not in fact therapeutic goods as defined in the Act. In short, subsection 7(1) provides a mechanism for clarifying whether particular goods or classes of goods are or are not therapeutic goods, and therefore whether or not those goods are subject to the regulatory scheme established by the Act.

In determining whether particular goods or classes of goods, or those goods when used, advertised, or presented for supply in a particular way, are therapeutic goods, subsection 7(1A) of the Act provides that the Secretary must disregard paragraphs (e) and (f) of the definition of 'therapeutic goods' in subsection 3(1). Paragraph (e) refers to goods for which there is a standard under subsection 4(1) of the *Food Standards Australia New Zealand Act 1991*, with the effect that those goods are excluded from the definition of therapeutic goods for the purposes of the Act. Similarly, paragraph (f) refers to goods which have a tradition of use as foods for humans in the form in which they are presented, with the effect of excluding goods which have a tradition of use as foods from the definition of therapeutic goods for the purposes of the Act. Accordingly, subsection 7(1A) has the purpose and effect of ensuring that an order declaring goods to be therapeutic goods under section 7 of the Act may bring certain goods within the scope of the Act, notwithstanding any food standard that may otherwise apply to those goods, or whether those goods have a tradition of use as foods.

The instrument amends the *Therapeutic Goods (Declared Goods) Order 2019* by declaring certain goods containing folate substances ("the relevant goods") to be therapeutic goods when used, advertised, or presented for supply for therapeutic use, or in a way that is likely to be taken to be for therapeutic use.

The instrument clarifies that the relevant goods are therapeutic goods as defined by the Act and therefore subject to the national system of controls established by the Act. This measure addresses uncertainty about the proper characterisation of the relevant goods as a consequence of the *Australia New Zealand Food Standards Code* – Standard 2.9.5 – Food for special medical purposes ("Food Standard 2.9.5"). The effect of the instrument is to confirm that the relevant goods are therapeutic goods for the purposes of the Act, irrespective of any view regarding the application of Food Standard 2.9.5 to the relevant goods prior to the making of this instrument.

Human rights implications

The instrument engages the right to health in Article 12 of the International Covenant on Economic, Social and Cultural rights ("ICESCR"). Article 12 of the ICESCR promotes the right of all individuals to enjoy the highest attainable standards of physical and mental health.

In General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12) (2000), the United Nations Committee on Economic, Social and Cultural Rights states that health is a 'fundamental human right indispensable for the exercise of other human rights', and that the right to health is not to be understood as the right to be healthy, but includes the right to a system of health protection which provides equal opportunity for people to enjoy the highest attainable level of health.

The instrument takes positive steps to promote the right to health by clarifying that the relevant goods are indeed therapeutic goods appropriately regulated under the Act. As a consequence, the instrument promotes public health and safety by ensuring the relevant goods are subject to the national system of controls provided under the Act relating to the quality, safety, and efficacy of therapeutic goods.

Conclusion

This instrument is compatible with human rights because it promotes the right to health in Article 12 of the ICESCR and otherwise does not raise any other human rights issues.

Dr Jane Cook, delegate of the Secretary of the Department of Health

Therapeutic Goods (Declared Goods) Order 2019

I, John Skerritt, as delegate of the Secretary of the Department of Health, make the following order.

Dated

Adjunct Professor John Skerritt
Deputy Secretary
Health Products Regulation Group
Department of Health

Contents

1 Name

This instrument is the *Therapeutic Goods (Declared Goods) Order 2019*.

2 Commencement

(1) Each provision of this instrument specified in column 1 of the table commences, or is taken to have commenced, in accordance with column 2 of the table. Any other statement in column 2 has effect according to its terms.

Commencement information		
Column 1	**Column 2**	**Column 3**
Provisions	**Commencement**	**Date/Details**
1. The whole of this instrument	The day after this instrument is made.	

Note: This table relates only to the provisions of this instrument as originally made. It will not be amended to deal with any later amendments of this instrument.

(2) Any information in column 3 of the table is not part of this instrument. Information may be inserted in this column, or information in it may be edited, in any published version of this instrument.

3 Authority

This instrument is made under section 7 of the *Therapeutic Goods Act 1989*.

4 Definitions

Note: A number of expressions used in this instrument are defined in section 3 of the Act, including the following:

(a) advertise;
(b) presentation;
(c) supply;
(d) therapeutic goods; and
(e) therapeutic use.

In this instrument:

Act means *Therapeutic Goods Act 1989*.

5 Declared goods—therapeutic goods

The goods or classes of goods specified in Schedule 1 to this instrument are declared to be therapeutic goods.

6 Declared goods—therapeutic goods when used, advertised, or presented for supply in a particular way

The goods or classes of goods specified in column 2 of an item in the table in Schedule 2 to this instrument, when used, advertised, or presented for supply, in a way specified in column 3 of that item, are declared to be therapeutic goods.

7 Declared goods—not therapeutic goods

The goods or classes of goods specified in Schedule 3 to this instrument are declared not to be therapeutic goods.

8 Declared goods—not therapeutic goods when used, advertised, or presented for supply in a particular way

The goods or classes of goods specified in column 2 of an item in the table in Schedule 4 to this instrument, when used, advertised, or presented for supply, in a way specified in column 3 of that item, are declared not to be therapeutic goods.

Schedule 1—Therapeutic goods

Note: See section 5.

Note This Schedule is reserved for future use.

Schedule 2—Therapeutic goods when used, advertised, or presented for supply in a particular way

Note: See section 6.

Goods that are therapeutic goods when used, advertised, or presented for supply, in a particular way

Column 1 Item	Column 2 Goods or classes of goods	Column 3 Use, advertising or presentation
1	goods that: (a) contain one or more of the following folate substances: (i) folic acid; or (ii) folinic acid; or (iii) levomefolic acid; or (iv) any other form of folate that may be characterised as an active principle, precursor, derivative, salt, ester, ether or stereoisomer; and (b) are represented as being food for special medical purposes, or being for dietary management of a disease disorder or medical condition; whether or not the recommended single dose of the goods contains sufficient macronutrients to feed, either exclusively or partially, the person for whom the dose is intended	when the goods are: (a) used, advertised, or presented for supply, for therapeutic use; or (b) used, advertised, or presented for supply, in a way that is likely to be taken to be for therapeutic use; including, but not limited to, one or more of the following therapeutic uses: (c) preventing, curing or alleviating depression; (d) curing or alleviating an inborn error of metabolism; (e) preventing, curing or alleviating folate deficiency; and that therapeutic use can be taken to relate to a folate substance mentioned in paragraph (a) in column 2 to this item

Schedule 3—Not therapeutic goods

Note: See section 7.

Note This Schedule is reserved for future use.

Schedule 4—Not therapeutic goods when used, advertised, or presented for supply in a particular way

Note: See section 8.

Note This Schedule is reserved for future use.

GEDDES, Jane

From: RC
Sent: Friday, 4 October 2019 4:13 PM
To: s22 [redacted]
Subject: Consultation: Proposed clarification that goods are therapeutic goods [SEC=OFFICIAL]
Attachments: Complaint_to_TGA_Neurofolin_Medical_Food_for_Depression.pdf; FOI 1225 Document 2 AR (Neurofolin).pdf; FOI request concerning previous complaint about Neurofolin.pdf; MoodDisordersCPGfinal.pdf; Firth_et_al-2019-World_Psychiatry.pdf

Dear s22 [redacted]

Thank you for your submission to the TGA's public consultation process on the proposed clarification that goods are therapeutic goods – goods containing folate substances in certain circumstances.

We invite you to make comments to us on the *attached* documents (as follows) we have received during the consultation process which may be relevant to the delegate's consideration of whether to make a declaration under s 7 of the *Therapeutic Goods Act 1989*:

- Complaint received from Dr Ken Harvey, Medreach Pty Ltd, Dr Harvey's FOI request to the Department of Health (the TGA) and document disclosed to Dr Harvey to comply with the request
- Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (2015)
- Firth et al – *The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials* World Psychiatry 2019; 18:308-324

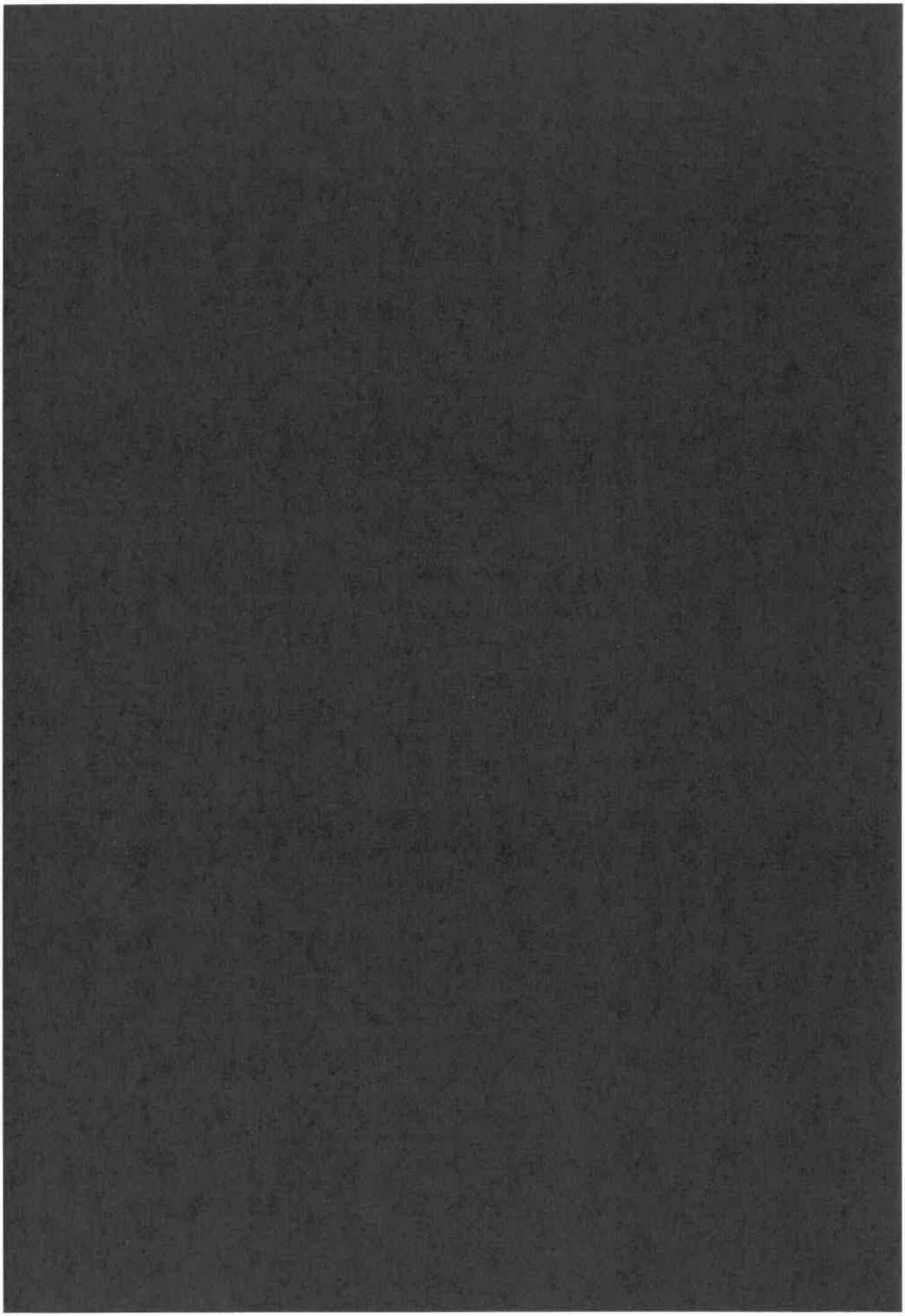
You are requested to please give us your comments by close of business on Friday 11 October 2019.

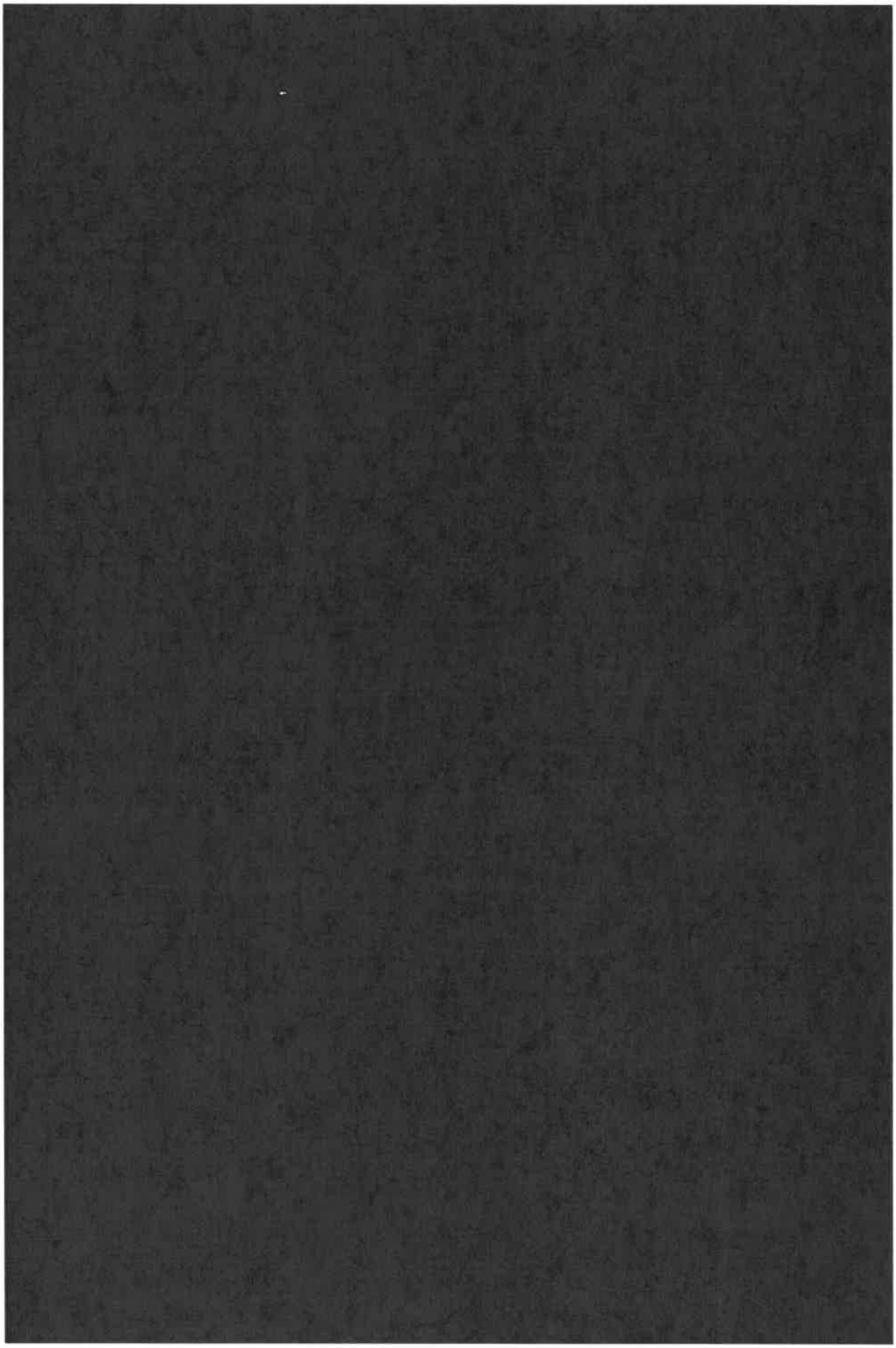
Regards,

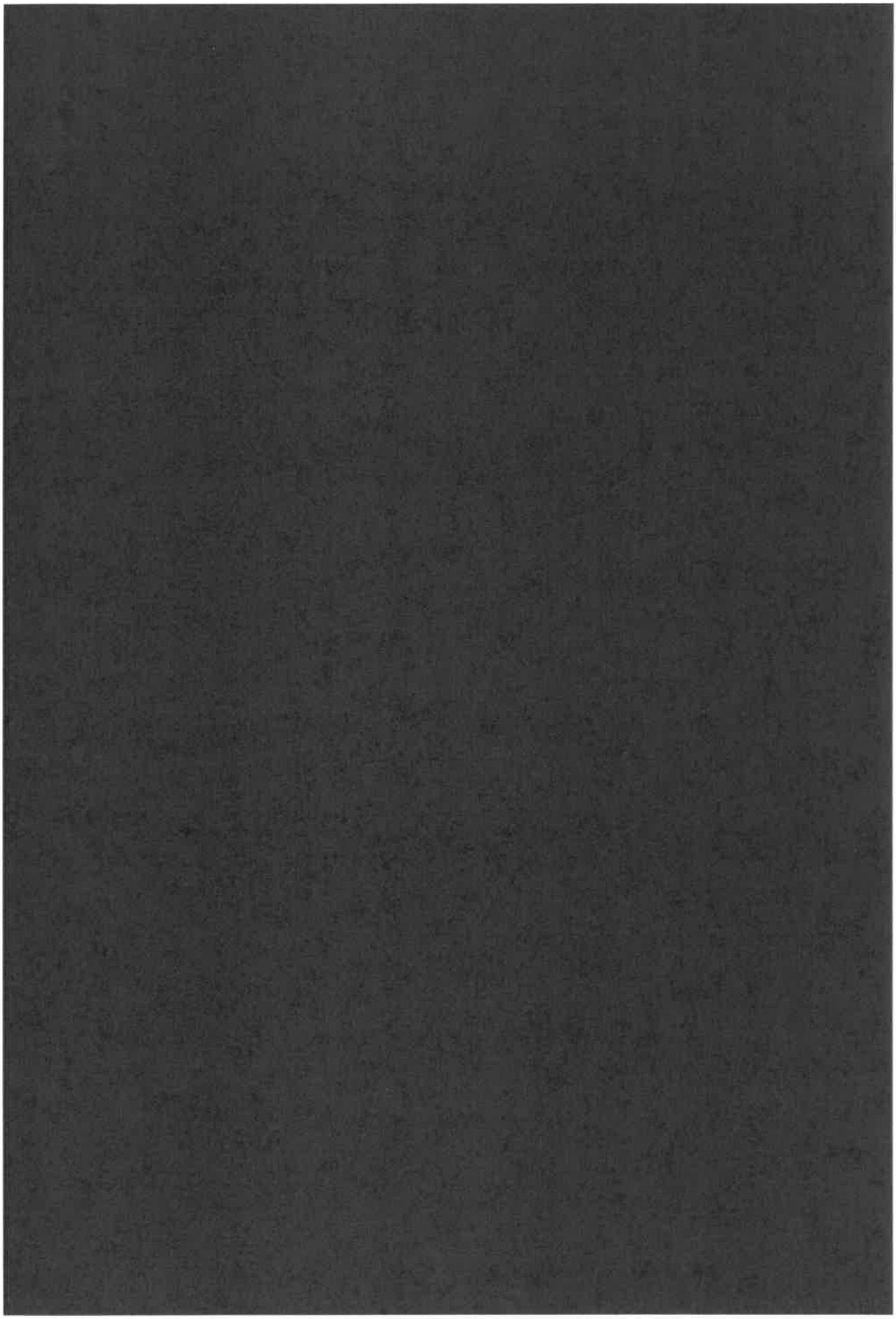
s22 [redacted]
[redacted]
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

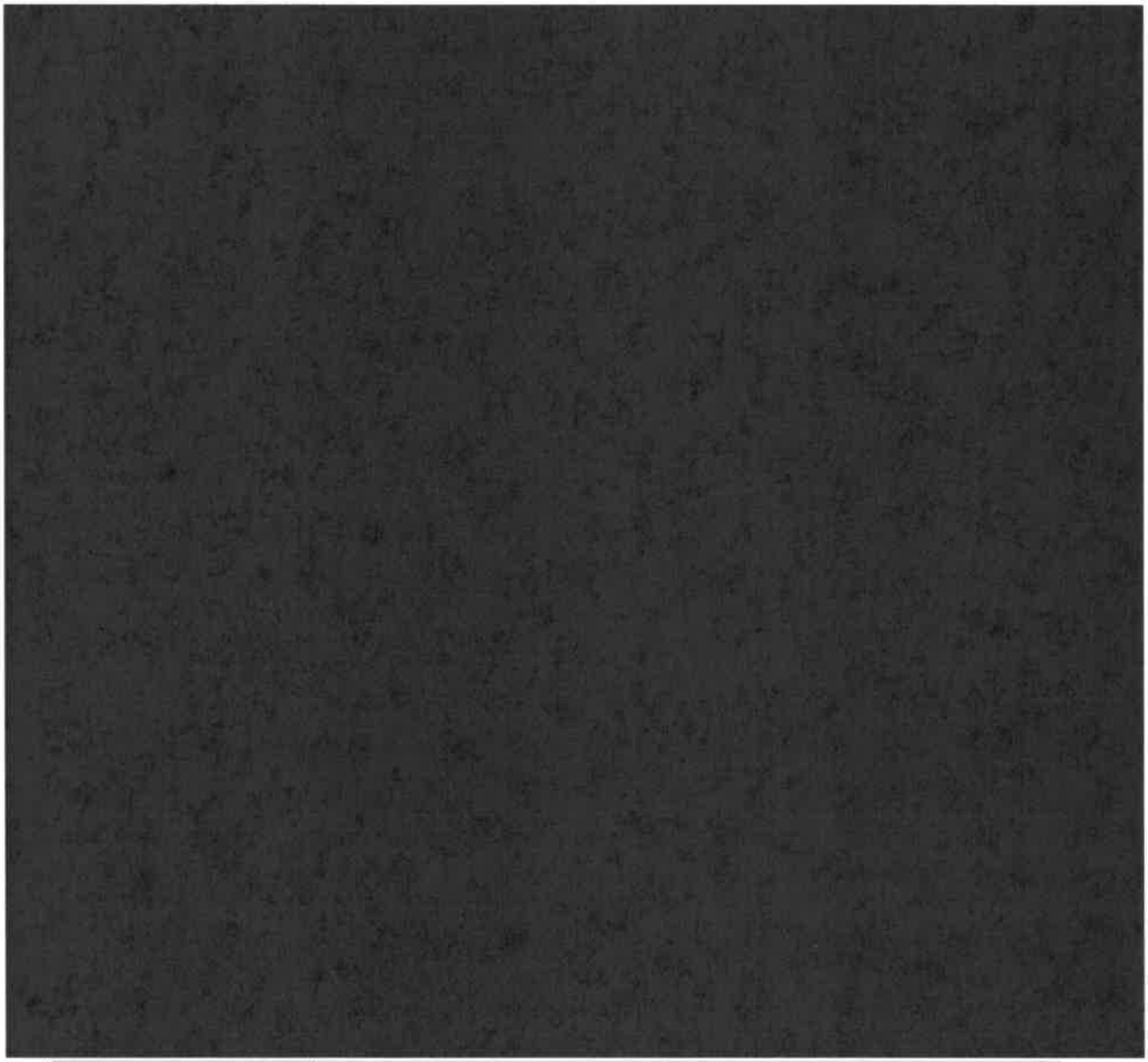
Phone s22 [redacted]
Email: RC@health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au









[redacted]
Sent: Tuesday, 29 May 2018 7:45 AM
To: KELLY, Larry
Cc: SKERRITT, John; MCRAE, Cheryl; BOOTES, Adrian; FRANCIS, Jenny
Subject: Neurofolin- a medicine being amrketed as a food? [DLM=For-Official-Use-Only]

Dear Larry

I picked up the attached from a counter in the Priceline pharmacy in Manuka.

I will bring the original to TGA,

Mylan are marketing a relative of folic acid as being "specially formulated for the dietary support in the management of depression."

Note that the presentation is in packs of 30 sachets each containing 15mg of L-methylfolate.

There is a stated dose- Take one sachet daily.

"Neurofolin should only be used under medical supervision"

"Neurofolin is only available in pharmacies and can be purchased without a prescription"

I downloaded one of the referenced papers (attached).

Its description of the action of L-methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food.

I think. prima facie, Mylan are distributing an unregistered therapeutic good.

To touch on a recent conversation we had, I suggest that this is not an advertising matter.

Rather, I suggest it is a breach of 19 D(1) of the TG Act and perhaps a "try-on" by Mylan.
Happy to discuss as needed

Frequently asked questions

Why has my doctor recommended Neurofolin?

Your doctor may have recommended Neurofolin to you to help support your dietary support in the management of depression

It can be taken together with your current antidepressant therapy or alone, as advised by your healthcare professional

How is Neurofolin different to tablets containing L-methylfolate?

Unlike some tablet formulations, Neurofolin has been specifically formulated for the dietary support in the management of depression with 15 mg of L-methylfolate

How is Neurofolin different from folic acid?

L-methylfolate is an active form of folate that is used by the brain to contribute to normal psychological function. Unlike folic acid, it does not require further metabolism before it can enter the brain.

How do I take Neurofolin?

Neurofolin is provided in packages of 30 sachets (one month's supply). Sachets should be completely dissolved in 200 ml of plain water (may be chilled) by stirring vigorously for 30 seconds. Drink immediately after preparation. Neurofolin should form part of a normal healthy diet. It is not suitable as a sole source of nutrition, or for children under 12

How much should I take?

Take one sachet daily

Where can I purchase Neurofolin?

Neurofolin is only available in pharmacies and can be purchased without a prescription. Please speak to your pharmacist

Where should I go for more information?

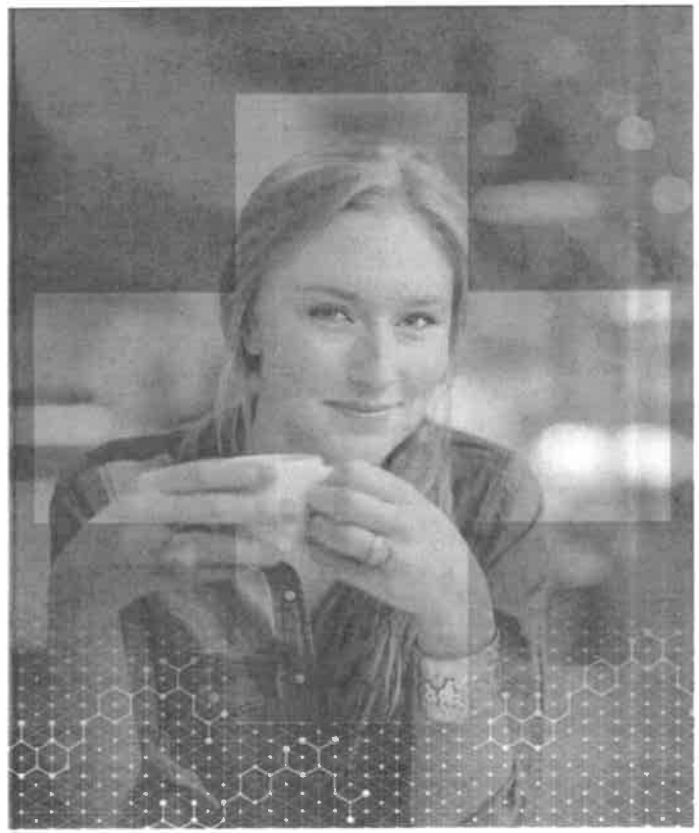
If you have any questions about Neurofolin, ask your doctor or pharmacist.

For more information call **Mylan** on **1800 314 527**.
Find out more at **neurofolin.com.au**

Neurofolin is for the dietary support in the management of depression and should be used under medical supervision.

References: 1. Miller AL. The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review: a Journal of Clinical Therapeutics.* 2008;13(3):216-226. **2.** Stahl SM. L-methylfolate: a vitamin for your monoamines. *The Journal of Clinical Psychiatry.* 2008;69(9):1352-1353. **3.** Barchas JD, Altemus M. Monoamine hypotheses of mood disorders. In: Siegel GJ Agranoff BW, Albers RW, *et al.*, editors. *Basic Neurochemistry:Molecular, Cellular and Medical Aspects. 6th edition.* Philadelphia: Lippincott-Raven; 1999.

GRUNBIOTICS Mylan



Neurofolin®

For dietary support in the management of depression

Neurofolin should only be used under medical supervision.
Find out more at **neurofolin.com.au**

GRUNBIOTICS Mylan

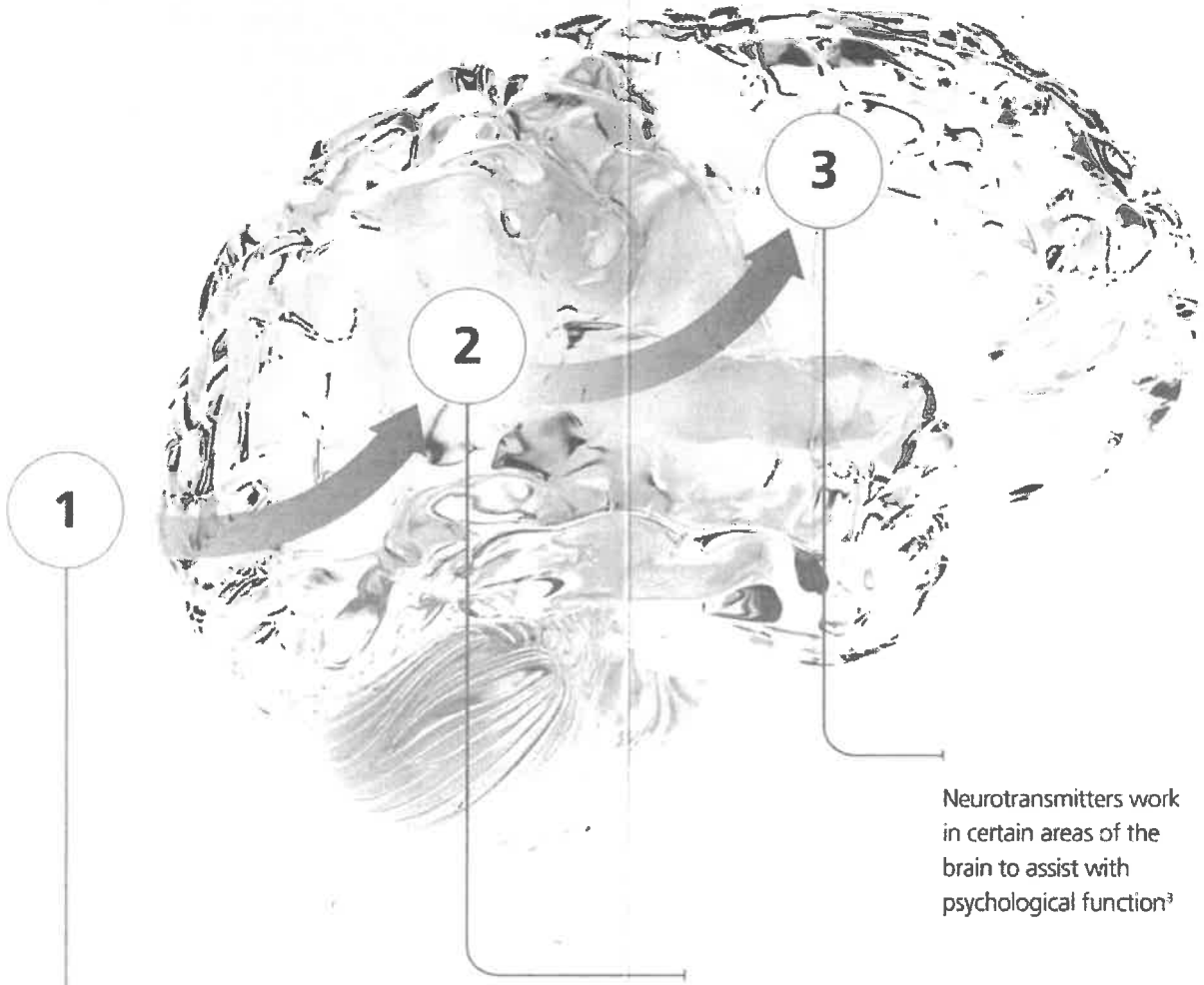
What is **Neurofolin?**

Neurofolin contains 15 mg of L-methylfolate, and is a food for special medical purposes to support the dietary management of depression.

L-methylfolate contributes to the production of some neurotransmitters, which in turn, assist in normal psychological function.[1,2]

Neurofolin should only be used under medical supervision.

How does **Neurofolin** work?



Neurofolin works by first entering the brain

Once in the brain, Neurofolin contributes to the normal production of some neurotransmitters[2]

Neurotransmitters work in certain areas of the brain to assist with psychological function[3]

GRUNBIOTICS Mylan

BRAINSTORMS
Clinical Neuroscience
Update

L-Methylfolate: A Vitamin for Your Monoamines

Stephen M. Stahl, M.D., Ph.D.

Issue: *Synthesis of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine is regulated by L-methylfolate, a derivate of the vitamin folate.*

Folate (vitamin B_9) is well known as one of the 13 essential vitamins, but perhaps what is not as well known is that a derivative of folate—known as L-methylfolate—is actually the active form of the vitamin.[1-3] One of L-methylfolate's critical roles is to regulate the synthesis of the 3 monoamine neurotransmitters serotonin, dopamine, and norepinephrine.[1-6]

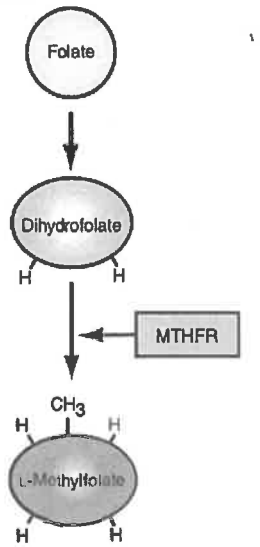
What Is L-Methylfolate?

Folic acid is the synthetic form of the vitamin folate and is present in artificially enriched foods such as bread and in over-the-counter multivitamins as well as in prescription vitamins.[3] Dihydrofolate is the dietary form of folate, derived from green vegetables, yeast, egg yolk, liver, and kidney.[3] A key regulatory enzyme known as methylene tetrahydrofolate reductase or MTHFR (Figure 1)[1-7] converts folic acid or dihydrofolate to a usable form in the body, L-methylfolate, that can then pass through the blood-brain barrier where it modulates the formation of the monoamines serotonin, norepinephrine, and dopamine.[1-7]

How Does L-Methylfolate Regulate the Synthesis of Monoamines?

L-Methylfolate acts to modulate the synthesis of monoamines in a 3-step process (Figure 2). First, L-methylfolate assists in the formation of a critical cofactor, known as tetrahydrobiopterin, or BH4 (Figure 2A), for the synthesis of monoamines.[4-6] Second, BH4 activates the rate-limiting enzymes tyrosine hydroxylase and tryptophan hydroxylase for the synthesis of monoamines.[4-6] Note that when these enzymes lack BH4 (shown as an empty "4" in the blue tyrosine hydroxylase and tryptophan hydroxylase enzymes

Figure 1. Synthesis of L-Methylfolate From Folate



Abbreviations: C = carbon, H = hydrogen, MTHFR = methylene tetrahydrofolate reductase.

Figure 2. Regulation of Monoamine Synthesis by L-Methylfolate

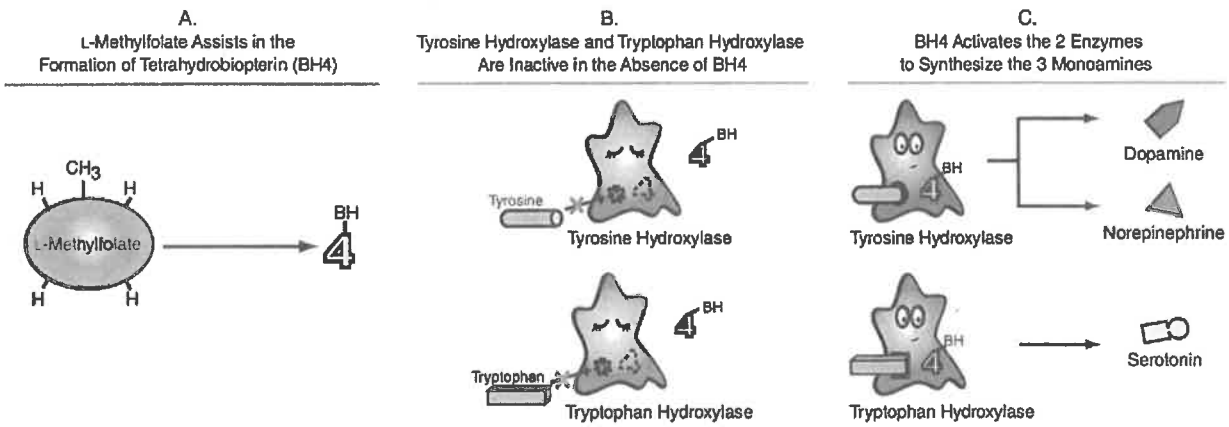


Table 1. Characteristics of Patients With Depression Who Might Be the Best Candidates for L-Methylfolate Treatment

Documented low levels of folate and its active metabolites such as L-methylfolate
Inadequate responses to a standard antidepressant
High risk for low folate levels resulting from
• Alcoholism
• Eating disorders
• Pregnancy
• Gastrointestinal disorders
• Documented low levels of MTHFR (methylene tetrahydrofolate reductase) or being from a group (Hispanic and Mediterranean populations) at high risk for decreased levels of this enzyme
• Documented high homocysteine levels, which tend to rise when folate falls
• Drugs that can interfere with folate conversion to L-methylfolate such as lamotrigine and valproate
Preference for a natural product approach with few or no side effects

Take-Home Points

- L-Methylfolate is the centrally active derivate of the vitamin folate and is utilized not only for neurotransmitter synthesis, but also for many vital methylation reactions in all cells.
- L-Methylfolate regulates the availability of the critical enzyme cofactor BH4 (tetrahydrobiopterin), required by tryptophan hydroxylase for serotonin synthesis and by tyrosine hydroxylase for dopamine and norepinephrine synthesis.
- Low levels of folate and L-methylfolate are linked to some forms of depression and to some patients who fail to respond to antidepressants, suggesting that augmentation of antidepressants with L-methylfolate may be a useful treatment option in these cases.

in Figure 2B), they are inactive and cannot bind to their amino acid substrates, tyrosine and tryptophan, which are the precursors for the monoamines. Third and finally, when L-methylfolate forms the critical amount of BH4, BH4 can activate these enzymes (Figure 2C), and tyrosine hydroxylase and tryptophan hydroxylase can now form the trimonoamines serotonin, norepinephrine, and dopamine.[4-6] Specifically, tyrosine can now bind with tyrosine hydroxylase and ultimately be converted into both dopamine and norepinephrine, and tryptophan can now bind with tryptophan hydroxylase and ultimately be converted into serotonin.

Therapeutic Implications?

One practical application of the central action of L-methylfolate may be for depressed patients who have inadequate monoamine neurotransmitter synthesis, especially if caused by an actual or functional deficiency in brain L-methylfolate (Table 1).[1-8] In such cases, administration of L-methylfolate could theoretically boost monoamine synthesis to the necessary levels and either treat depression or boost the therapeutic action of antidepressants dependent upon adequate levels of monoamines.

So, who might be the best candidates to receive L-methylfolate? Research is still trying to answer this question, but the current evidence suggests that the best candidates for L-methylfolate treatment might be depressed patients who have documented low levels of folate and its active metabolites, including L-methylfolate, and who fail to respond to treatment with a standard antidepressant.[1,8] Investigators are also determining whether those at risk for low L-methylfolate levels, such as those who have certain concomitant illnesses, have certain genetic risk factors for low L-methylfolate levels due to inheritance of low MTHFR enzyme activity, or are taking certain drugs that interfere with L-methylfolate formation (Table 1), might also be responsive to antidepressant augmentation with L-methylfolate.[1,8]

Summary

L-Methylfolate modulates the synthesis of the monoamines serotonin, norepinephrine, and dopamine. Some depressed patients may have their disorder or their lack of response to an antidepressant linked to low levels of folate and L-methylfolate. Research is currently working to establish which patients with depression would be the best candidates for L-methylfolate treatment. ◆

References

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8. Gilbody S, Lightfoot T, Shelton T. Is low folate a risk factor for depression? a meta-analysis and exploration of heterogeneity. J Epidemiol Community Health 2007 July;61(7):631–637

Brainstorms is a section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, Brainstorms, Neuroscience Education Institute, 1930 Palomar Point Way, Ste. 101, Carlsbad, CA 92009.

Australian Government

Department of Health

Request for access to documents under the *Freedom of Information Act 1982* (Cth)

The Department of Health (Health) does not generally hold personal health records about individuals such as; medical practitioner notes, hospital records, pathology and other diagnostic test results or allied health practitioner records. Such documents may be obtained either directly from an individual's practitioner, or relevant private hospital.
State/Territory public health records may be sought through State/Territory Freedom of Information processes. Details of other processes can be found on the relevant State/Territory health department website.

Applicant's Details

Title	Dr
Surname	Harvey
Given name	Ken
Company/Representative (if applicable)	
Postal Address	35a Mary St, Hawthorn, Vic 3122
Email and Telephone	ken.harvey@medreach.com.au 0419181910

Documents requested

I request access to the previous complaint about Neurofolin mentioned in the email below.

From: TGA Advertising <tga.advertising@tga.gov.au>
Sent: Tuesday, 21 May 2019 15:45
To: 'ken.harvey@medreach.com.au' <ken.harvey@medreach.com.au>
Subject: RE: TGA complaint: Neurofolin, AC-NLDGK2LY/2019 [SEC=OFFICIAL]

Dear Dr Harvey

Thank you for your submission of a complaint through the TGA Advertising Complaints Handling portal on 14 May 2019 in relation to Neurofolin and follow up email dated 16 May 2019.

The TGA has **previously received a complaint regarding the product Neurofolin** and there is an open case being managed by the Regulatory Compliance Section (RCS).

As such, this complaint has been referred to the RCS for information and a separate case **will not be opened by the advertising team.** You will shortly receive the automated acknowledgement and close out email for your complaint.

Kind Regards,

Advertising Compliance Unit
Email: tga.advertising@tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

The applicant's preferred means of accessing the documents identified above is:

- To receive a copy by post ☐
- To receive a copy by email ☒
- To inspect the documents at the office of Health ☐

Consultation with third parties

If the documents identified relate to an individual/organisation (other than the applicant) it may be necessary for Health to consult that individual/organisation in order to obtain their views about the potential release of documents.

Where consultation with a third party is necessary:

- the client/ applicant consents to the disclosure of their identity for the purposes of third-party consultation.

  Yes ☐ No ☒

FOI Charges

The costs relating to FOI requests for other documents, such as policy documents or reports, are determined by the *Freedom of Information (Charges) Regulations 1982.* Where considered appropriate an estimate of charges will be provided to you by Health.

Response received 9/10/2019 9:45 pm [redacted]

Dear Sasha,

I can't comment on the attached materials. They are too technical. I can only say that for my particular chemistry Neurofolin benefits me. I am taking 30 milligrams of Lexapro and still found myself

extremely depressed last year. It was a horrible feeling. In desperation I went to the Chemist in [redacted] and asked about the item in the window advertised to help depression. I was given a starter packet and noticed remarkably soon that I was no longer in that very dark place I had been in only days before. It was kind of amazing.

Subsequent results haven't been that drastic after taking it fairly regularly but I do notice when I stop taking it. My only blood irregularity historically has been slightly enlarged red blood cells and as I vaguely recall the chemical makeup of Neurofolin can shrink red blood cells??? So that they can be absorbed in the area of the brain that makes serotonin?? Sorry if I have misunderstood this.

In any case feel free to call me if you wish.

Kind Regards,

[redacted]

Response received 14/10/2019 6:27 pm [redacted]

Dear [redacted],

I am writing to provide comments on the documents I received from you on October 4 2019 as part of the TGA's public consultation on a proposed declaration under s 7 of the Therapeutic Goods Act 1989. I am happy for my comments to be published on the TGA's website with my name and contact details (which are at the end of this letter) redacted.

These documents do not change my view that products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes serve the needs of current consumers.

RANZCP Guidelines

In relation to the RANZCP Guidelines, Table 17 on p 45 refers to 'Folate (including L-Methylfolate)' in a table headed 'Complementary therapies for depression'. The table entry states 'may assist depressive symptoms as adjunct to prescription medication'. Page 46 states 'several of the more commonly used complementary therapies used to assist mood are summarised in Table 17'.

I do not think that this reference to folate or L-methylfolate would mean that people in the community are more likely to interpret Neurofolin as being a substitute for prescription medicine. To my mind, the use of the word 'therapy' does not change the fact that the RANZCP Guidelines make clear that folate or L-Methylfolate may be used in conjunction with treatments that have therapeutic value. Folate or L-methylfolate may be used to support such treatments, but I do not interpret the RANZCP Guidelines as suggesting that it is a treatment in its own right. I do not think anything contained in the RANZCP Guidelines provides a robust argument against the correct classification of Neurofolin as a Food for Special Medical Purposes.

Firth et al, Efficacy and safety of nutrient supplements

The Firth article's overarching conclusion is that there is a strong relationship between nutrition and mental disorders and there is a growing acknowledgement of this relationship within the community. This article also sets outs the results of a number of clinical trials that examine the effects of a high dose of methylfolateas an adjunctive treatment for mental disorders and concludes that there are benefits for depressive symptoms. Within the context of this paper's discussion of nutrition and its benefits and the clear lack of detrimental side effects of methylfolate this does not suggest a therapeutic mechanism of action.

Complaint dated 29 May 2018

This document sets out some details about Neurofolin and refers to a referenced paper, and continues that the paper's 'description of the action of L-Methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food'.

I do not agree with this statement. Even if the paper attached to the complaint does not describe L-methylfolate using the word 'food', it describes it as a 'derivative of the vitamin folate'. In my view vitamins are one of the key components of foods, and folate is found in many everyday foods.

Every nutrient in food can be shown to have some kind of effect at a physiological level; e.g. Vitamin C or water.

Complaint from Dr Ken Harvey dated 19 May 2019

This complaint does not change my view that Neurofolin should be available for sale as a FSMP and I would make the following observations about this document:

- it appears to be a broader complaint about products in the FSMP category and targets Neurofolin as just one of a number of examples;

- it states that there is insufficient evidence that L-methylfolate is an adjunctive or sole therapy for depression, however this does not appear to be consistent with the RANZCP Guidelines or the Firth article provided;

- it lists a number of claims about Neurofolin as being 'misleading or deceptive' but having read those claims I do not agree with this statement;

- it says that consumers with depression do not have a medically determined nutrient requirement for L-Methylfolate, however my understanding is that there is evidence that depression and low folate levels are linked in many patients;

- it quotes an incorrect reference to the relevant "Food for Special Medical purposes" standard in the Food Standards Code.

This is a lengthy document and I am making these comments in general but have not been given particular parts about which the TGA is seeking my views. I would be able to provide more specific comments if provided with particular references.

Yours Sincerely,

s22 [redacted]

s22 [redacted]

Response received 17/10/2019 12:02 pm

s22

Dear s22 ,

Please find my comments attached. It is a lengthy read and I did try to keep it as short as possible. I hope that the comments are useful and I hope that the outcome does not lead to Neurofolin's removal from the Australian market as this will be extremely detrimental, as highlighted in my submission.

I think you will find through this submission that contrary to Dr Harvey's submission, there is an important role for Neurofolin as a food for special medical purposes.

Please keep me posted on the outcome.

Many thanks

s22

TGA SUBMISSION

Consultation: Proposed clarification that goods are therapeutic goods- goods containing folate substances in certain circumstances

Source: https://www.tga.gov.au/consultation/consultation-proposed-clarification-goods-are-therapeutic-goods-goods-containing-folate-substances-certain-circumstances

s22 [redacted]

It is with thanks to the Therapeutic Goods Administration (TGA), other submitters, Associate Professor Dr. Ken Harvey and his private consultancy company, *Medreach PTY LTD*, that I make this submission to the TGA pertaining to the above proposed clarification. In particular, I acknowledge Dr. Harvey's role in the betterment of the Australian health landscape through rigid analysis of Government policies affecting various Australian health policies and regulations, as well as his role as the *President of Friends of Science in Medicine,* who strive to ensure therapeutic goods and services are ethically promoted to the general public.

In response to the email dated 04/10/19 from Sasha Barclay of the *Regulatory Compliance Section of the TGA*, I have opted to take the opportunity to make relevant comments on the documents attached to the original email, which include:

- Complaint received from Dr Harvey.
- Dr. Harvey's FOI request to the TGA and documents disclosed to Dr. Harvey.
- The Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for mood disorders
- The peer-reviewed article by *Firth et al: The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry 2019; 18:308--324*

I emphasise that this submission is merely a comment on the above documents and not an extensive literature review as to the clinical efficacy of folate, folic acid or L-methylfolate however, I did review the literature and commented below with evidence as to the role of L-methylfolate.

Additionally, I have included a referenced list of citations that may be of assistance to the delegate, in the decision-making process.

All references are accessible online or via specialised access portals (e.g. Tertiary Institution Subscriptions) however, should a document be of interest, I am happy to forward such documents to the delegate with consideration for the relevant copyright laws.

I would like to disclose my qualifications as a Community Pharmacist s22 [redacted] medical student. I *do not* own a pharmacy and I am a casual employee at various pharmacies, in which I *do not* receive commission for any sales, including complementary medications. Additionally, I have *not received* any funding or renumeration for this submission from any person, party or organisation. I make this submission in the interest of science and patient outcomes.

DISCUSSION

I agree principally with Dr Harvey's submission on the following issues:

1. The separation of the Food Standards Australia New Zealand (FSANZ) and the Therapeutic Goods Australia (TGA) creates a complex and inconsistent environment in which sponsors of products are left to navigate a tremulous regulatory terrain in product approval and subsequent marketing to the general public. A model like the United States Food and Drug Administration (FDA) is the direction Australia should be heading towards, especially as there is an important nexus between food and drugs.

I present the following comments, and evidence:

2. Folate, folic acid and L-5-methyltetrahydrofolate are not the same thing.[1, 2]
    a. Folate and folic acid: [3]
        i. Folate = naturally occurring form of Vitamin B9, in food.
        ii. Folic acid = synthetic form of Vitamin B9: in fortified food, supplements and pharmaceutical preparations.
        iii. Folate and folic acid are structurally similar.
    b. Levomefolate calcium: [4]
        i. Also known as: L-MTHF; L-5MTHF; L-methylfolate; Levomefolate calcium
        ii. L-MTHF = metabolically active form of Vitamin B9, after conversion by the enzyme Methylenetetrahydrofolate reductase (MTHFR).

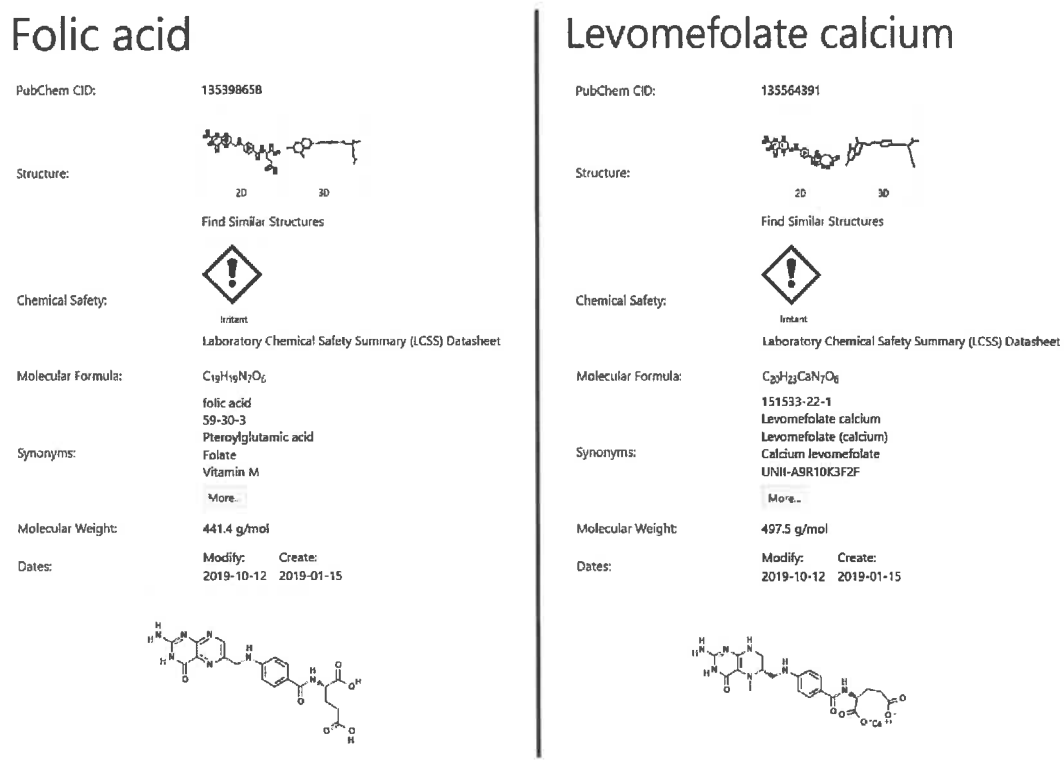

Figure 1. Structural differences between Folic acid and Levomefolate calcium [3, 4]

3. *ARTG 270098*, a listed product containing L-MTHF and sponsored by *RN Labs PTY LTD*, is available at 500mcg strength whereas *Neurofolin®* is L-MTHF at 15mg.[5]

   a. ARTG 270098 highlights that permitted indications include:

      i. *"Maintain/support (state vitamin/mineral) within normal range".*
      ii. *"Maintain/support cognitive function/mental function".*
      iii. *"Aid/assist/helps synthesis of neurotransmitters".*
      iv. *"Maintain/support nervous system function".*

   b. ARTG 270098 highlights that indication requirements include:

      i. *"Product presentation must not imply or refer to mental illnesses, disorders or conditions."*

   c. The two sections, I believe, are contradictory in nature as mental illnesses are a complex combination of impairment in mental function, impairment in neurotransmitter signalling and impairment in nervous system function.

   d. Perhaps a change in packaging by *Neurofolin®* sponsors is sufficient to alleviate the basis of the complaint.

4. Mental illnesses are regarded as restricted representations by the *Therapeutic Goods Act 1989*, however: [6]

   a. *Neurofolin® is not currently governed by the above ACT, limiting the claim of a breach in TGA Advertising Code (No.2) 2018.*[7]

   b. *TGA Advertising Code (No.2) 2018, Part 4- Restricted representations and prohibited representations, 28(1)(a)* states:

> (1) Subject to subsection (2), for the purposes of section 42DD of the Act, a form of a disease, condition, ailment or defect is a serious form if:
>
> (a) it is medically accepted that the form requires diagnosis or treatment or supervision by a suitably qualified health professional, except where the form has been medically diagnosed and medically accepted as being suitable for self-treatment and management; or
>
> (b) there is a diagnostic (including screening), preventative, monitoring, susceptibility or pre-disposition test available for the form (including a self-administered test), which requires medical interpretation or follow-up.

      i. *Neurofolin®* marketing material is consistent with this exemption as it explicitly states in the product pamphlet *"as advised by your healthcare professional"*, as well as the text on their website FAQ *"must be used under the guidance of a healthcare professional"*, thus indicating a diagnosis had to have been made.
      ii. Additionally, *the Royal Australian and New Zealand College of Psychiatrists (RANZCP)* includes folate supplementation as an accepted complementary therapy for depression (like St John's Wort, as an example) however, the extent of the evaluation in limited.[8]

5. The food standard highlighted in Dr Harvey's submission was incorrectly indicated as FSANZ 2.6.5 however, it should be FSANZ 2.9.5.[9]

6. There ***is*** evidence to support L-MTHF at 15mg for use as an adjuvant to antidepressants in the management of depression.

    a. It is important to highlight that this is not definitive evidence of L-MTHF effectiveness but in the spirit of scholarly debate regarding this matter, it is good evidence of the use of L-MTHF at 15mg. I would emphasise however that further studies are necessary.

    b. I do not agree that the cited metanalysis and systematic review disprove the usefulness of L-MTHF as an adjuvant to antidepressants (see dot point *"Studies Cited by Dr. Harvey"*), but instead, are at the very least, early evidence suggesting effectiveness.

    c. A key study cited by Dr. Harvey is a 2012 RCT by Papakostas et al.[10]

        i. The authors highlight that this was the first study of its kind, in 2012.
            - It indicates that L-MTHF is well tolerated, not "ill tolerated" as per Dr. Harvey's submission.
            - Was only evaluated with SSRIs, one of many classes of antidepressants.
            - Concludes that 15mg/day, not 7.5mg/day of adjuvant L-MTHF may be an effective and safe augmentation strategy for patients with MDD for patients on SSRIs. This is the dose used in *Neurofolin®.*
            - Commentary by Roberts, S et al (2013) highlights that additional research is required however, the use of L-MTHF, as opposed to folic acid, is a strength of the study.[11]

        ii. A subsequent follow-up study in 2016 that involved Papakostas, and three of the original authors of the 2012 study, indicates that L-MTHF at 15mg/day is an early option in patients who failed to achieve an adequate response to monotherapy antidepressants (SSRIs in particular). Additionally, they conclude that preliminary evidence suggested sustained remission and sustained recovery.[12]
            - The study emphasises that L-MTHF is safe, well tolerated and allowed the sample group to achieve a high rate of response, remission and recovery.
            - Of note is the limited sample size of this study (n=68)

        iii. A commentary discussing the role of pharmacogenetics, and referencing the above study, as well many others, highlights the complex nature of genetic polymorphisms that contribute to major depressive disorders (MDD) and similarly suggest that the role of L-MTHF needs to be seriously considered and, the data from Papakostas et al. (2012) study need to be replicated.[13]

d. Gerald, M (2017) synthesises the literature well in relation to the role of L-MTHF in the management of depression by augmentation of SSRI and SNRI. There are various studies cited within that indicate both the difference of L-MTHF from folic acid, and the role folate supplementation plays, proposing that it should be part of standard routine clinical practice.[14]

e. At the time of writing, there are up to 20 RCT studies and case reports, not metanalysis or systematic reviews, that support the use of L-MTHF.

   i. The issue with studying such a product is the complex nature of MDD including variability in genetic, genomic and environmental factors faced by the target population thus, such studies cannot simply be discounted due to a small sample group but instead, should form the basis for additional, large scale, well designed, randomised-controlled trials.

   ii. I believe that the scientific approach to proving effectiveness often counterintuitively halts the future development and discovery of interventions, especially when professionals in the fields of research only give weight to findings from large sample groups.

      - PubMed search string used:
        "(L-MTHF[Title/Abstract] OR L-5MTHF[Title/Abstract] OR L-methylfolate[Title/Abstract] OR Levomefolate calcium[Title/Abstract]) AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh])"

7. Neurofolin® advertising claims are not in breach of Australian Consumer Law as at the time of writing, they abide with FSANZ 2.9.5 requirements.[9] However, further expert opinion may be explored to determine if there is in fact a breach.

8. I am unable to comment on other products, including Souvanaid®, Ceretain® and Neurothrive® however I agree that the ability for sponsors to self-declare under FSANZ 2.9.5 may present complications. This is beyond the scope of this consultation or my submission.

9. FSANZ 2.9.5 – Definitions[9]; indicates:

> (1) In this Code:
>
> ***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.

a. This highlights digestion and metabolism as a requirement, which is consistent with evidence suggesting that Methylenetetrahydrofolate reductase (MTHFR) C677T genotype limits the conversion of folate to biologically active L-MTHF and thus, dietary management cannot be completely achieved without the use of the food.

i. A 2017 Australian meta-analysis of ten folate intervention studies assessing the impact of MTHFR C677T genotype on serum folate levels confirms that patients with this genotype have lowered serum folate levels.[15]

- Note that this study does not focus on MTHFR genotypes in depression but instead on the impact on folate levels in general.

ii. The above findings are consistent with a 2015 systematic review and meta-analysis of trials and observational studies, finding that lower blood folate levels are found in populations with the MTHFR C677T genotype.[16]

- This analysis however only included on women aged 12-49 years only.[16]

iii. Several other meta-analysis and systematic reviews explore this relationship pertaining to various medical conditions, but are not cited.

- See PubMed with search string: *("Methylenetetrahydrofolate Reductase (NADPH2)"[Mesh]) AND ("Folic Acid"[Mesh])*

b. Is used under medical supervision, as supported by RANZCP guidelines as well as the consumer information material for *Neurofolin®*.[8]

10. The National Health Measures Survey (NHMS) data referencing < 1% of women aged 16-44 had low folate is relating particularly to neural tube defects (NTDs), not relating to major depressive disorders (MDD). Additionally, MDD has an estimated prevalence of 4% in 12-months of the Australian population, thus such data is not useful in evaluating folate levels of people with MDD.[17]

11. The Academy of Nutrition and Dietetics findings and recommendations that dietary interventions are not needed for patients with MTHFR gene mutations are particularly relating to cardiovascular health, regarding homocysteine levels, not for mental health or any other conditions, including NTDs.

12. Studies cited by Dr. Harvey:

a. The cited studies (original references in Dr. Harvey's submission were 12,13,14) that do not support the use of folic acid for the treatment or prevention of depression utilised folic acid, not L-MTHF.[18-20]

- **i.** This is explicitly mentioned in Okereke et al (2015) and in fact, the author states that L-MTHF did reduce depression severity in patients with MDD.[20]
- **ii.** As highlighted earlier, they are not the same thing, thus the findings are not translatable.
- **iii.** Additionally, the dosage of folic acid used were 400ug in two studies and 1.5mg in the third study. Both dosages are not anywhere close to the 15mg/day of L-MTHF used in *Neurofolin®*.

b. The Mollehave et al (2017) study cited utilises Mendelian Randomisation (MR) in its methodology.[21]

- **i.** The study concludes that there is no causal effect of circulating folate on the overall risk of depression however, they highlight that the small to moderate effects observed cannot be discounted and warrant further, larger scale studies.
- **ii.** MR analysis is based on two population studies of the Danish population, rather than analysing meta-analysis or systematic reviews or RCTs on the subject.
- **iii.** MR are considered novel approaches to epidemiological study design but aim to address confounding factors and reverse causality that may be present in specifically, observational studies, not RCT's, meta-analysis or systematic review. MR studies are not considered superior to RCTs and have specific limitations including insufficient statistical power, confounding (in the form of linkage disequilibrium and population stratification), pleiotropy, and canalization and gene-environment interactions. Basically, this limits their utility in determining the effectiveness as the risk allele (MTHFR C677T genotype) needs to be strongly associated with the intermediate factor being investigated otherwise, the validity is questionable.[22]

c. The video referred to in Dr. Harvey's complaint (which is as of writing is unavailable online) cites a 2013 peer-reviewed study by Shelton et al. (2013), that employed *Naturalistic Observation* research methodology, showing 67.9% of participants (n=376) responded to treatment with L-MTHF as an adjuvant to antidepressant therapy.[23]

   i. Naturalistic Observation is a formal scientific, qualitative, non-experimental research methodology aimed at capturing experiences of patients using a treatment in their own environment. It is nonexperimental in nature however; no manipulation of the patient's environment occurs. The specific utility of such a study is both in animal and human behaviour. The results provide insight to psychologists, anthropologists and social scientists in ascertaining certain behaviours that are not under a simulated experimental design, as with quantitative methodology. The benefits include yielding behavioural changes that are otherwise immeasurable by RCT's.[24]
   ii. A key limitation of such study designs is that the findings are not necessarily representative of the generalised population and as such, are usually followed up by qualitative methods, such as RCTs (the gold standard).[24]
   iii. In line with the literature highlighted above, I view that this study design is valid, given that additional RCT's, metanalysis and systematic analysis show evidence of the effectiveness of 15mg of L-MTHF as an adjuvant to antidepressants in patients with MDD.

d. Schefft et al. (2017) performed a systematic review and meta-analysis using search terms that omitted L-MTHF (in all its naming variations), and only used traditional terms, such as Folic acid. However, it was still able to identify studies based on L-MTHF.[25]

   i. Of the 8 studies evaluated, only two pertained to L-MTHF, both of which are the above RCT's by Papakostas et al. (2012).[10]
   ii. Schefft et al. (2017) indicates that larger samples are required, though does not discount the findings of the effect of 15mg of L-MTHF citing that there is *"too little data to draw a firm conclusion".*[25]

e. Firth et al. (2019), the most recently available systematic review and meta-analysis, only evaluated two key studies pertaining to L-MTHF at the optimal dose of 15mg, as is the case in *Neurofolin®*: Godfrey et al (1990) and two Papakostas et al. (2012) studies.[10, 26-28] This was achieved by utilising an earlier systematic review and meta-analysis by Roberts et al. (2018).[29]

   i. The findings relating to Papakostas et al. (2012) studies are discussed above.
   ii. The Godfrey et al. (1990) study I would consider dated, though the findings are still relevant and valid in support of 15mg of L-MTHF.[27]
   iii. Final analysis in the Firth et al. (2019) and Roberts et al. (2018) combine folate and L-MTHF, which as highlighted earlier, are not the same product.[1-4, 26, 29]
   iv. Despite this, they indicate that there is "favour" and a "recommendation" towards L-MTHF supplementation at 15mg/day, not the sub-optimal 7.5mg, with a moderate to large benefits for the former dose.[26, 29]
   v. Concluding remarks discount the overall effects of folate *after* excluding the trials based on 15mg/day.[26]

13. RANZCP Mood Disorder guidelines: [8]

   a. Lists folate as a valid and important investigation in the medical work-up of the presenting patient, indicating its importance for this population group.

   b. Lists L-MTHF, as a complementary therapy that "may assist depressive symptoms as adjunct to prescription medication".

   c. These findings are based on a systematic review and meta-analysis of RCT trials by Taylor et al. (2004) and a systematic review by Sylvia et al. (2013), the former explicitly states that *"current available evidence suggests that folate supplementation may be effective when used in addition to conventional antidepressant medication"* while the latter states that *"a small but significant improvement was noted in depressive symptoms"*.[30, 31]

14. Given the above array of evidence, and the critique of the counterevidence, I believe that there is evidence that justify the use of 15mg/day of L-MTHF in select populations suffering from MDD, under the guidance and supervision of specialist psychiatrists.

15. In my personal practice as a pharmacist, and involvement in the mental health units throughout my medical training, an upwards of 50 patients have been initiated on L-MTHF with good effect. Many of my pharmacist colleagues report similar findings in their patient groups however, I concede that this is not scientific evidence and merely anecdotal.

16. I view that the potential ramifications of reclassifying Neurofolin® as proposed will highly likely lead to the sponsor withdrawing the product from the Australian market, as the TGA registration process is unreasonably expensive and complex.

a. This will have an impact on patients that have been well stabilised in my personal practice and abroad, since the release of *Neurofolin®.* The potential to exacerbate their mood disorders is very real and should be a serious consideration in regard to this consultation.

b. Patients will seek other means of accessing products containing L-MTHF, including online purchases from the USA, Canada, UK and Europe, at higher costs (adding financial burden) and with the extremely high risk of consuming products that are not governed by Food Standards Australia or the TGA.

17. It is worth noting, though beyond the scope of this submission, that a recent Australian trial, named the 'SMILES' trial, investigated the impact of diet on major depressive episodes. This showed early preliminary findings that with a modified Mediterranean diet, mental health appears to improve in MDD. This diet consisted of a diverse mix of foods, one of which is 60mL of olive oil/week.[32] How will the TGA respond when a sponsor in the future begins marketing specially formulated olive oil for mood disorders? Will there be another consultation? The future of health and nexus with dietary importance is growing and rapidly changing. This needs to be taken into consideration further enforcing Dr. Harvey's point regarding the double standards involved when two bodies (FSANZ and TGA) exist to regulate medication and foods.

SUMMARY OF COMMENT

A. FSANZ and TGA existing as separate bodies creates a complex environment for patients, practitioners, medical researchers and product sponsors. An FDA model is the ideal scenario.

B. Folic acid and L-MTHF are not the same ingredient, and any literature review and considerations pertaining to this consultation should treat them with distinction.

C. There are no other products currently available that have 15mg of L-MTHF, except *Neurofolin®* and the *RN Labs PTY LTD ARTG 270098* item is distinct.

D. Changes in packaging requirements by *Neurofolin®* sponsors may be sufficient in addressing the consultation.

E. *Neurofolin®* is not governed by the TGA however, even with consideration, the marketing material is consistent with *TGA Advertising Code (No.2) 2018.*

F. There is good evidence, including RCT's, systematic reviews and meta-analysis and case-reports that L-MTHF at 15mg/day, as the active ingredient in *Neurofolin®*, has a role as adjuvant to antidepressants in MDD.

G. A large portion of the literature cited by Dr. Harvey in his submission in fact conclude that L-MTHF at 15mg/day is useful as adjuvant to antidepressants in MDD, as they do not adequately distinguish between folic acid and L-MTHF.

H. There is an absence of substantial evidence, though there is good evidence, regarding the effectiveness of L-MTHF at 15mg/day, owing to limitations in the number of studies, but this does not disprove or discount the currently available evidence.

I. Neurofolin® advertising claims are not in breach of Australian Consumer Law, in my limited experience regarding this field.

J. MTHFR C677T genotype is an established factor in the literature limiting the conversion of folic acid to biologically active L-MTHF, thus dietary management with a food for special medical purposes is required.

K. The complex nature of scientific literature and the limitations of studies including methodology should always be thoroughly considered in such consultations, including all the studies I have cited.

L. The literature is often circular in referencing as evidenced by the limited range of studies that are recycled in the systematic reviews however, the evidence should not necessarily be discounted as non-existent.

M. Both Naturalistic Observation studies and Mendelian Randomisation have strengths and weaknesses that should be considered when reviewing the literature.

N. RANZCP guidelines support the use of L-MTHF at 15mg/day, based on their cited studies.

O. The most likely consequence of the outcome of this consultation is withdrawal of *Neurofolin®* by the sponsor from the Australian market, which will significantly disadvantage already stabilised patients, as well as limiting access to new patients.

P. Patients will seek other means of accessing products, which will likely be from online purchases and their safety cannot be guaranteed.

The views and opinions expressed in this commentary are my views when evaluating the literature and do not necessarily reflect the official position of any person, group, profession or organisation.

This document was compiled in the spirit of science, and the betterment of the Australian healthcare landscape. It is not intended to discredit or attack at any individual or organisation.

All references are available in PDF format upon request

I thank you for the opportunity to comment on this consultation.

Warm regards,

s22 [redacted]

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Response received 17/10/2019 5:39 pm s22

Dear s22

I am writing to provide comments on the documents I received from you on October 4 2019 as part of the TGA's public consultation on a proposed declaration under s 7 of the Therapeutic Goods Act 1989. I am happy for my comments to be published on the TGA's website with my name and contact details (which are at the end of this letter) redacted.

These documents do not change my view that Neurofolin is correctly characterised as a Food for Special Medical Purpose. I believe Neurofolin is a nutritional product for dietary management and not for the treatment of a disease. This Food for Special Medical Purpose has no other comparable product available in Australia and without it many people will be unnecessarily disadvantaged.

RANZCP Guidelines

In relation to the RANZCP Guidelines, Table 17 on p 45 refers to 'Folate (including L-Methylfolate)' in a table headed 'Complementary therapies for depression'. The table entry states 'may assist depressive symptoms as adjunct to prescription medication'. Page 46 states 'several of the more commonly used complementary therapies used to assist mood are summarised in Table 17'.

I do not think that this reference to folate or L-methylfolate would mean that people in the community are more likely to interpret Neurofolin as being a substitute for prescription medicine. To my mind, the use of the word 'therapy' does not change the fact that the RANZCP Guidelines make clear that folate or L-Methylfolate may be used in conjunction with treatments that have therapeutic value. Folate or L-methylfolate may be used to support such treatments, but I do not interpret the RANZCP Guidelines as suggesting that it is a treatment in its own right. I do not think anything contained in the RANZCP Guidelines provides a robust argument against the correct classification of Neurofolin as a Food for Special Medical Purposes.

Firth et al, Efficacy and safety of nutrient supplements

The Firth article's overarching conclusion is that there is a strong relationship between nutrition and mental disorders and there is a growing acknowledgement of this relationship within the community. This article also sets outs the results of a number of clinical trials that examine the effects of a high dose of methylfolate as an adjunctive treatment for mental disorders and concludes that there are benefits for depressive symptoms. Within the context of this paper's discussion of nutrition and its benefits and the clear lack of detrimental side effects of methylfolate this does not suggest a therapeutic mechanism of action.

Complaint dated 29 May 2018

This document sets out some details about Neurofolin and refers to a referenced paper, and continues that the paper's 'description of the action of L-Methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food'.

I do not agree with this statement. Even if the paper attached to the complaint does not describe L-methylfolate using the word 'food', it describes it as a 'derivative of the vitamin folate'. In my view vitamins are one of the key components of foods, and folate is found in many everyday foods.

Every nutrient in food can be shown to have some kind of effect at a physiological level; e.g. Vitamin C or water.

Complaint from Dr Ken Harvey dated 19 May 2019 as well as most recent article sent:

As stated in a separate email to you I do not think Ken Harvey's complaint nor opinion should be any more heavily weighted than that of qualified and respected scientists and medical professionals. Ken Harvey's negative bias towards is well recognised and is documented in a formal study critically analysing Friends of Science in Medicine's (Ken Harvey's organisation) media to determine if power and ideology are deployed in their representation of T&CM and FSMPs and concludes: " The Friends of Science in Medicine represent complementary medicine through a strategy of rhetoric and argumentation that contradicts the literature. Their discourse is symbolic and derives from a power-based ideological perspective that forms the basis for promoting exclusion of complementary medicine from university education and primary health care..."

This complaint does not change my view that Neurofolin should be available for sale as a FSMP and I would make the following observations about this document:

· it appears to be a broader complaint about products in the FSMP category and targets Neurofolin as just one of a number of examples;

· it states that there is insufficient evidence that L-methylfolate is an adjunctive or sole therapy for depression, however this does not appear to be consistent with the RANZCP Guidelines or the Firth article provided;

· it lists a number of claims about Neurofolin as being 'misleading or deceptive but having read those claims I do not agree with this statement;

· it says that consumers with depression do not have a medically determined nutrient requirement for L-Methylfolate, however my understanding is that there is evidence that depression and low folate levels are linked in many patients;

· it quotes an incorrect reference to the relevant "Food for Special Medical purposes" standard in the Food Standards Code.

This is a lengthy document and I am making these comments in general but have not been given particular parts about which the TGA is seeking my views. The many emails received throughout the process also added to the confusion on what it was that the TGA wanted comment on.

Yours Sincerely,

s22 [redacted]

s22 [redacted]

Email: s22 [redacted]

Response received 17/10/2019 6:10 pm s22

Dear s22

RE: Consultation: Proposed clarification that goods are therapeutic goods

Thank you for your invitation to comment on some submissions and documents relating to the above. The information provided is extensive and has been challenging to assess in the short timeframe available. s22 . I apologise for the delay in my response.

The information provided would be enhanced by a statement on conflict of interest by Dr Harvey that detailed his personal and professional interest in this matter and provided information on the source of his income including for research projects. I would welcome this information.

Please note that this response is for the TGA only.

I wish to comment on the complaint from Dr Harvey. I note that by his stated qualifications Dr Harvey is a Pathologist. He is not a Psychiatrist (or even a pharmacologist or statistician) yet he seems to ignore or reject the expert advice of such experts in this field and expresses personal, unqualified opinions despite the available evidence (including evidence in highly respected refereed medical journals). Dr Harvey provides little supporting evidence for his opinions, appears to contradict himself a number of times in his complaint and to have read the publications selectively.

Dr Harvey's main issue appears to be with the food medicine interface, he strongly asserts that "product sponsors" should not be able to self determine food for special medical purposes without independent assessment - as is permitted under current regulations. If this is his complaint he should address it it in its own right and separately. It is inappropriate that he uses neurofolin to drive his objective to the potential detriment of consumers who find it helpful.

Grun Biotics has only ever claimed that neurofolin is for dietary support in management of depression. It has never claimed that it is anything more. It is not a therapeutic good or a complementary medicine and to declare it as such would be grossly misleading. Dr Harvey completely misses the point when he rejects a significant study because 91% of the subjects were also receiving a conventional antidepressant. This is precisely the population that neurofolin attempts to assist and for which there is evidence to support its use. Neurofolin is not for use alone. It is for dietary support of medication. That neurofolin is an adjunct, not a therapeutic good or complementary medicine is further affirmed by the RANZCP and Firth in the references referred to us by the TGA.

Neurofolin is classified as a food for special medical purposes. A number of arguments that Dr Harvey proffers make the assumption that neurofolin is not. Therefore the arguments do not apply.

I am informed that Grun Biotics has requested advice from the FDA on a number of occasions regarding any specific concerns that it has regarding neurofolin being classified as FSMP or any aspect relating to it but to no avail. I believe that this is highly irregular and reprehensible and should be rectified as soon as possible. I understand that the forms of Lmehylfolate used for the same purposes as neurofolin overseas are classified as FSMP or its equivalent.

Neurofolin may not work for every person in this complex field but there is evidence that it does benefit a substantial number of the people who use it. Further, I personally am aware of a number of friends and acquaintances (including family members) who use neurofolin in conjunction with their medication and believe it has made a significant contribution to their improved health and wellbeing.

The approach taken by TGA not only disrespects consumers who use and benefit from neurofolin, it places at risk, through delay and uncertainty, an innovative Australian company committed to assisting sufferers of depression.

I urge you not issue the proposed order. I consider that such an action would be inappropriate, unjustified and cause unnecessary harm.

Sincerely

s22 [redacted]

Response received 20/10/2019 4:36 pm s22

Dear s22,

RE: Consultation: Proposed clarification that goods are therapeutic goods

I refer to the article "A controlled trial of homocysteine lowering and cognitive performance", McMahon et al, submitted by Dr Harvey, which you forwarded late on 15thOctober and which I have only now received at the end of an international flight.

I do not believe that the article has any relevance to your enquiry whatsoever. It relates to cognitive decline not depression and makes no reference to depression. My understanding is that, more commonly, depression is not necessarily related to cognitive decline and cognitive decline is not necessarily related to depression. The article makes no reference to how many (if any) of the subjects also suffered from depression.

Furthermore the results of the study are highly predictable. Had the result been positive, folates would probably have been the most highly sought after product in the world as cognitive decline commences early in all people's lives! The only redeeming feature of the study is that it found that subjects experienced no harm or side effects from folate.

I do not understand what the TGA is on about. It appears that action is being considered following a complaint by one inexpert and unqualified individual despite an overwhelming body of expert evidence and opinion. The irrelevance of the article referred to above further reinforces this concern.

The issue as I understand it is whether neurofolin is food for special medical purposes or a therapeutic good. Ample evidence and opinion has been provided to demonstrate that it is a dietary adjunct to support medication for depression. It is not a therapeutic good in its own right and it would be grossly misleading to suggest so by classification.

Sincerely

s22

Response received 18/10/2019 9:09 am s22 [redacted]

Dear s22 [redacted],

s22 [redacted] would like to make the following comments on the documents that you provided.

An FSMP is typically a food provided to people who have a limited ability to digest, absorb or metabolise certain regular foods and therefore are reliant on a sole or partial diet of specially formulated products for adequate nutrition.

The Food standards code definition of FSMP from standard 2.9.5 – Food for special medical purposes is as follows:

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.

Therefore FSMP products are intended for the exclusive or partial feeding of people with limited or impaired capacity to consume, digest, absorb or metabolize ordinary foodstuffs or certain nutrients contained therein, or who have other special medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet.

The formulation of foods for special medical purposes should be based on sound medical and nutritional principles. Their use should have been demonstrated, by scientific evidence, to be safe and beneficial in meeting the nutritional requirements of the persons for whom they are intended.

The purpose of FSMP products is for dietary management to help patients meet their nutritional requirements.

We have the following comment on the Neurofolin product that is the subject of the complaint.

- The product only provides 2 micronutrients (15mg of L-methylfolate and 1mg of vitamin B12) with no other nutritional content/support.

- While the Food Standards Code does not mandate nutritional composition requirements for FSMP that are not a sole source of nutrition, it would be expected that a non-nutritionally complete FSMP to contain significant quantities of the nutrient that have been added to help achieve the dietary management of the condition specified. The Neurofolin product contains only 2 vitamins and no significant level of any macronutrient.

- The RDI of folate is 400 micrograms per day. The folate level of this product looks excessively high compared to the amount needed for dietary management. If there are people who have a folate metabolism disorder and cannot meet their daily dietary requirements of folate from food alone then there may be a legitimate reason to have an FSMP product containing L-methylfolate. However the level of L-methylfolate would be expected to be closer to the RDI for folate and not many times above it.

- It appears from the product formulation (only 2 vitamins and no macronutrients, plus and an apparently very high level of L-methyl folate) that the product is not designed for dietary management for nutritional support but for some other purpose.

An FSMP product that is intended to be consumed under medical supervision for the "dietary management" of a disease, disorder or medical condition must not 'refer to the prevention, diagnosis, cure or alleviation of a disease, disorder or condition'.

An FSMP product may provide more than the RDI of certain vitamins and minerals, especially if that FSMP is designed for or use as a sole source of nutrition.

Even if claims are not made, an FSMP product should not be including vitamins or minerals at levels many times above that of the RDI unless it has been demonstrated, by scientific evidence, to be necessary, safe and beneficial in meeting the nutritional requirements of the persons for whom they are intended.

It appears that L-Methyl folate has a dietary folate equivalent similar to folic acid. If this is the case 15mg of l-methyl folate would provide many times the RDI of folate, far in excess of any normal dietary requirement.

It is possible that products covered by the food standard for FSMP could feasibly have the same formulation as a therapeutic good. However if an FSMP product makes or implies claims that are beyond dietary management of a disease, disorder or medical condition then it could become an illegal FSMP product or an illegal therapeutic good.

We consider a claim of "nutritionally support mood regulation" as a claim that should not be made by a FSMP product. This claim states or implies that that product has a therapeutic action to regulate mood. Mood regulation would not have any special medically determined nutrition requirement and mood regulation appears to be a therapeutic claim.

A claim of 'for dietary support in the management of depression' for an FSMP product would only make sense if there are specific medically determined nutrient requirements for people with depression that cannot be achieved through a normal healthy diet.

Folic acid is an essential nutrient and as such there is a legitimate place for an FSMP product to include folate for dietary management of some diseases. For example many foods high in folate are not permitted on the very low protein diet for people with inborn errors of protein metabolism. Therefore some patients with inborn errors of protein metabolism need to use FSMP products to provide the majority of the protein and micronutrient requirements (including folate).

In these cases dietary management of a disease is appropriate to help people meet their special medically determined dietary requirements. Claims of curing or alleviating an inborn error or metabolism in an FSMP product should never be made – only reference to the dietary/nutritional support.

People unable to meet their dietary intake of folate from a normal diet, or with low / suboptimal folate, or with congenital errors of folate metabolism may benefit from L-methyl folate. An FSMP

product could provide L-methyl folate for dietary/nutritional support but not make or infer any therapeutic claims.

By formulation, Neurofolin with 15mg of methyl-folate seems to contain many times over the RDI of folate and appears to present therapeutic levels of methyl-folate. If this is the case the product looks like it is not designed to provide dietary/nutritional support but rather formulated to provide an amount of L-Methyl folate consistent with evidence of therapeutic use for relief of depression symptoms and mood regulation, which are therapeutic uses.

An FSMP product could be a food to help improve suboptimal folate levels in people with depression if it was demonstrated that people with depression may have special dietary needs including depressed levels of folate.

Any claims such as cognitive or mood enhancement, relief of symptoms of depression, or improvement of depression symptoms we regard as a therapeutic claim. Any claim or implied claim that an FSMP product is for the relief or alleviation of depression would be a therapeutic claim and would not be permitted for an FSMP product.

Thanks and Regards

s22 [redacted]

Response received 18/10/2019 11:54 pm [redacted]

Dear [redacted],

Please find attached my comments in response to your request for consultation. I am afraid due to my time commitments they are brief, however the majority of the relevant scientific literature was included in my initial comments submitted through the formal process on the 18/09/19.

If the TGA requires further consultation or expert advice, please feel free to contact [redacted]. We can certainly organize a time to provide a formal write up of the relevant literature to help you with your decision further.

I hope my comments are helpful in assisting you with your decision and given the enormous amount of evidence countering the merit of a section 7 declaration, hope that you do not proceed with it.

Best regards

[redacted].

Dear s22

Please find my response to your request for consultation on the section 7 declaration: *Proposed clarification that goods are therapeutic goods*. I find nothing in these documents which alter my previous opinion that the proposed section 7 declaration is inappropriate and should not proceed. The below comments are brief. Due to time constraints I am unable to provide the same detailed response to you that I did initially, however the key scientific literature was summarised in my initial communication request call for comment that closed on the 18/09/2019.

Regarding "Complaint to the TGA: Neurofolin - a food for special medical purposes for the dietary support of depression management".

This document involves a complaint from Dr Ken Harvey regarding the product Neurofolin® by the Australian company Grunbiotics. I summarise the key points and my comments on the matters below.

- Dr Harvey initially implies that it is inappropriate to refer to depression as a disease state in relation to Neurofolin® which is currently regulated as an FSMP, however bases this claim on TGA requirements which are not applicable.

The representation of a product cannot reasonably be judged based on the regulatory requirements of a different regulatory category. I am confused why Dr Harvey would take this approach initially, especially as it acknowledged these requirements are not relevant later in the same page.

- Dr Harvey alleges that Neurofolin® is not appropriately marketed as an FSMP under FSANZ Standard 2.6.5.

In this regard, I assume that Dr Harvey refers to FSANZ Standard 2.9.5. which relates to FSMPs as the one referenced does not appear to exist. It should also be noted that many quoted lines are not truly quotes from this standard, for example "food for medicinal purposes" is in fact "food for medical purposes". Although Dr Harvey is well known and respected by many, including myself, for his fight against pseudoscience, these obvious errors do raise concerns about whether he has the sufficient knowledge of this relatively niche area for much weight to be placed on his opinion. I can acknowledge that FSMPs can, prima facie, have similarities in some respect to pseudoscientific products. However, in practice it is a branch that can offer robust, well supported, and specific assistance to those who have an illness that requires a dietary management component. As a regulatory category they are distinct and should not be confused with either 'natural' or 'alternative' medicines.

- Dr Harvey also alleges that claims made in relation to Neurofolin® are in breach of Australian Consumer Law.

The basis of this is outside my expertise to robustly debate as I am not familiarly with Australian Consumer Law. However, it appears that many of the claims made in compliance with FSANZ Standard 2.9.5 and comparable to other manufacturers in the field. There are a few key claims that may require adjustment and I encourage the relevant regulatory bodies to discuss this matter of presentation with the company in particular.

- A further broader complaint is made about the nature of FSMPs and the ability of product sponsors to self-declare.

In this regard, I do agree with Dr Harvey, tighter regulation of the FSMP category in terms of gaining formal regulatory approval would be beneficial. Not only would it provide Australian companies the opportunity to confirm the appropriateness of their product, but it would provide additional protection to the Australian public. However, this in no way reflects on a specific product under the current regulatory guidelines. Rather it is a call for wider reform. Importantly, it doesn't argue that any specific product should be regarded as a medicine, but that the FSMP category receive better regulatory oversight.

- Dr Harvey provides page 2 as a series of links and claims from the website relating to Neurofolin®.

I question Dr Harvey's complaint about a claim which is reporting on a study. However, again, if there are concerns with the nature of the claims, this does not ipso facto make a product a therapeutic. It should be addressed at the presentation level unless there is evidence that the product functions as a therapeutic. There is still not evidence that the product does this.

- Dr Harvey provides a basic background regulatory definition for therapeutic goods and FSANZ Standard 2.9.5 (now correctly identified).

This appears accurate.

- Dr Harvey provides a background on folate and the measured levels in the Australian population.

This represents the status of healthy people – or at least that of the general population. It does not represent a specific diseased population and is therefore not very relevant to the discussion. Moreover, red blood cell folate may have little correlation on levels of key metabolites derived from folate in the brain depending on what comorbidities the individual has. In various disorders and mutations disrupting the metabolism and processing of folate, red blood cell levels may remain high, however levels in the cerebral spinal fluid remain very low.

- On page 4 Dr Harvey recognises that up to 70% of people with depression may have a specific polymorphism relating to a reduced ability to convert folate to l-methylfolate. He argues that 60 – 70% of the general population has variants in this gene and therefore challenges the data as meaningful.

Unfortunately, the evidence Dr Harvey cites is of an extremely low quality, being a short review that presents mixed evidence before presenting very solid conclusions with no reliable justification. To be frank, I am surprised this paper was accepted to be published. In regard to the numbers of patients in the general population affected, it also mixes multiple mutations in this statistic, likely greatly exaggerating the numbers in the general population. Frankly I am a little shocked Dr Harvey would pick this paper to try and support anything in this matter. From the top of my head I can think of papers which offer a substantially more rigorous investigation of the topic, for instance Girelli et al, 2003[1] found significant nutrient-gene associations between C677T mutations and folate status. This directly challenges Dr Harvey's report with far more reliable evidence. Moreover, it is entirely possible – even likely – that mutations in one gene will have little influence alone and may require other mutations to influence a disease state such as depression. The fact that it is a multifactorial genetic pathway that may result in a changed requirement for a vitamin does not make it less valid.

- Dr Harvey contends that a number of trials have found folate to be ineffective at modulating depression.

This is consistent with the argued mechanism of action with Neurofolin which contains not folate, but l-methylfolate, a biologically active form of folate that can bypass metabolic disorders, in other words, assisting with the dietary management of a disease state. This is the intended purpose of an FSMP.

- Dr Harvey discusses in depth the work by Papakostas G, et al. (2012). He notes that "L-Methylfolate was **Ill** tolerated, with rates of adverse events no different from those reported with placebo.".

I sincerely hope this is an unfortunate typo from Dr Harvey, the paper itself found that L-Methylfolate was "**well tolerated**".

- Dr Harvey notes that "there were methodological **limitations to these studies, including a relatively small** sample size, short treatment period and short duration of follow-up." **Dr Harvey also notes that high** dose folate can cause some health problems in **those with a history of colorectal cancer.**

In terms of a study finding statistical significance, these **are arguably only evidence of the suitability of adding L-**methylfolate to treatment resistant patients as it seems to **offer them support. While a favoured limitation of**

[1] https://academic.oup.com/jn/article/133/5/1281/4616756

graduate students to include in their thesis, complaints of small sample size and short testing periods are best used as a justification for failing to find significant differences, not the inverse. The note about colorectal cancer is odd, especially as Dr Harvey notes that the study used L-methylfolate, not synthetic folic acid or equivalent. Furthermore, if folate – or in this case L-methylfolate – is consumed as an FSMP, it is to be taken under medical supervision. The supervising clinician can advise patients with these risk factors to abstain. By making a product like Neurofolin inaccessible to the public, it is likely that many patients may access comparable products through less regulated means, receiving no medical supervision. This a strong argument to not proceed with the proposed section 7 declaration.

- Dr Harvey describes several other studies all generally supportive of L-methylfolate based dietary management in depression to assist along with actual therapeutic medication. Dr Harvey implies there could be a conflict of interest with the funding of some of these studies.

I agree that these studies are supportive. I also agree there is a potential conflict of interest due to funding. However, this does not negate the research without evidence that this conflict of interest resulted in ethical breaches. Given the niche nature of this research it is unsurprising to find industry support for the research and is the case for a large amount of translational research. This argument could be made in regard to this complaint also. Dr Harvey is the president of the Friends of Science in Medicine organisation and has a professional and reputational stake in arguing that products are inappropriately marketed. Just because Dr Harvey gains something from his actions, this does not invalidate his actions due to the potential conflict alone. The review by Schefft et al., 2017 adds nothing to this discussion as it fails to do any useful analysis with the data and does not look at other interesting data that directly relate. I have previously shared some of this data with the TGA along with far more robust papers doing meta-analyses which relate. It is true that the data mentioned by Schefft would be insufficient for a therapeutic. However, Neurofolin and comparable FSMPs are not therapeutics. It is an FSMP. The risk is well acknowledge as negligible while the benefit may exist for a few patients. The data requirements can and should be considered differently. The data presented here exceeds that presented by many other FSMPs and is a good justification for the status of Neurofolin® to remain as an FSMP.

- Dr Harvey argues that "Medically diagnosed depression does NOT have special medically determined nutrient requirement".

Numerous studies looking at populations of individuals diagnosed with depression have observed a significant deficit in folate levels in red blood cell and serum levels relative to the general population (Abou-Saleh & Coppen, 1989; Astorg et al., 2008; Morris, Fava, Jacques, Selhub, & Rosenberg, 2003; Ng, Feng, Niti, Kua, & Yap, 2009; Sánchez-Villegas et al., 2009). Approximately 30.4% to 64% of patients suffering from Major depressive disorder (MDD) display a red blood cell folate deficiency, with about 36% of depressed patients showing cerebral 5-MTHF deficiency (where serum folate levels are normal but cerebral spinal fluid 5-MTHF is low) (Bottiglieri et al., 2000; Farah & Farah, 2009; L. A. Pan et al., 2017). This relationship has been confirmed through multiple robust meta-analyses (the most reliable form of evidence) which have concluded a significant relationship between folate status and depression, even after adjusting for potential confounds (Bender, Hagan, & Kingston, 2017; Gilbody, Lightfoot, & Sheldon, 2007). Ambrosino et al., 2015 even found that 15mg of L-methylfolate was specifically helpful in correcting hyperhomocysteinemia as a marker of folate deficiency.

In this regards, Dr Harvey is clearly and unequivocally arguing **against** a considerable body of scientific literature.

- Dr Harvey goes on to discuss various claims made in the advertising of Neurofolin.

In relation to these claims I leave it up to the company to either justify or alter their presentation of the product. I have certainly already provided evidence to the TGA providing evidence for claims that Dr Harvey claims he has been unable to find. Whether these claims – even if supported by evidence – are suitable for marketing, is another question that I will not attempt to answer at the current time.

Conclusion

This complaint was overall disappointing for me to read. I have great respect for Dr Ken Harvey and his campaign against pseudoscience. However, this submitted complaint employs a very low bar of evidence where it

suits the authors agenda and ignores high quality evidence that does not. I strongly encourage the TGA to disregard this complaint where it relates to the data on depression and nutrition – specifically L-methylfolate. It has little basis in the empirical literature. **Moreover, nothing in this complaint suggests that Neurofolin or comparable products be regulated as therapeutics under a section 7 declaration.** In fact, the complaint almost argues the opposite, that this product should not even be considered an FSMP. While I disagree with this point, I fail to see how anything in this complaint justifies the proposed declaration.

Despite this, I do share Dr Harvey's sentiment that FSMPs should receive independent assessment and confirmation of status being placed on market for reasons described above. I believe better regulation in this category will resolve any concerns the TGA currently has over the status of products such as Neurofolin. It will also allow better control over the appropriate claims made around these products.

Regarding "The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials".

- The results section on pp 311 – 314 and Figure 2 of this article describe several articles examining the effect of folate and derivatives on unipolar depression, mostly major depressive disorder (MDD).

The reported data offers moderate support for managing the diet of patients diagnosed with these disorders with folate. I am cautious about accepting the findings of the few cited studies looking at folate supplementation, as other studies not cited have found no effect. The most convincing data, as noted in the paper, is that relating to using 15mg of L-methylfolate alongside approved therapeutic pharmaceutical medication. Overall this tangential data supporting that a dietary requirement for increased folate may exist in those diagnosed with these disorders. Importantly, these studies involve cases where the relevant folate or derivative is taken in conjunction with approved therapeutic pharmacological medication. The data in this article does not suggest that taking folate is an effective therapy for unipolar depression or MDD. The most reasonable interpretation is that this form of dietary management may assist by restoring levels of a vitamin required for normal function.

- The discussion section notes that most of the effect size was observed due to the robust nature of providing 15mg of L-methylfolate alongside approved therapeutic pharmaceutical medication. The paper notes that "Methylfolate is readily absorbed, overcoming any genetic predispositions towards folic acid malabsorption, and successfully crossing the blood-brain barrier".

This interpretation is consistent with my own above. It does not indicate that L-methyfolate should be used as a therapeutic for unipolar depression or MDD. Rather it suggests that patients with these disorders benefit from dietary management. An FSMP on the market to assist these patients that can be taken under the supervision of a medical professional would be an important addition to helping these patients obtain the best health possible.

Conclusion

If a product for therapeutic use, or in a or food presents itself in a way that is advertised or presented for supply way that is likely to be taken to be for therapeutic use, this should be addressed at the claims level for a specific product. The data presented in this article does not indicate that any form of the vitamin B9 is suitable as a therapeutic for unipolar depression or MDD. An overly broad section 7 declaration is wholly inconsistent with the data presented both here and the broader literature.

Regarding "Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders".

- Table 17 claims that folate (including L-methylfolate) my assist depressive symptoms as an adjunct to prescription medicine. It notes that there are no known hazards or interactions are that one should try dietary enhancement first.

The suggests a general acceptance that folate (in my opinion, specifically L-methylfolate) can benefit patients with depression. Indeed, it specifically suggests considering dietary enhancements before moving on to complementary therapies. An FSMP is an ideal food source for dietary enhancement where it relates to a specific disease. By employing a section 7 declaration and making all FSMPs that provide folate or a derivative and may be used for dietary management in depression therapeutics, you deprive patients of easy, safe, and affordable access the dietary enhancement recommended in these guidelines. As such, I again strongly oppose this notion.

- Page 46 talks generally about complementary medicines, especially those with a high cost. However, it notes that those that show some benefit, especially where the cost is low, and have no adverse effects, are worthwhile.

I have two key points in regard to this page, the sentiment of which I agree with overall. Foremost, the section 7 declaration proposed is not in relation to a complementary medicine, it is related to an FSMP. An affordable food-based product is ideal to assist patients to provide dietary management in relation to a disease. Secondly, the TGA should be careful with overreliance on the specific wording used in scientific and medical literature. Neither academics nor medical practitioners are regulatory experts. The use of the word "therapy" or phrase "complementary medicines" may not refer to a therapeutic or medicine in the strict sense defined by the *Therapeutic Goods Act 1989*. Rather it may just be a convenient term used to describe something that is beneficial for a specific population or a substance or activity not traditionally considered a medicine by the medical community.

Conclusion

The following sections identified in this document essentially offers an endorsement of an FSMP to help provide folate based dietary management/enhancement for patients with depression who require this dietary based modification. It is perhaps the best indication that the proposed S7 declaration is inappropriate.

Regarding "A Controlled Trial of Homocysteine Lowering and Cognitive Performance".

- The attached article is a study looking at lowering homocysteine in elderly patients. It tests homocysteine levels and cognition.

This article has little relevance to the proposed S7 declaration. What relevance it does have suggests that vitamins are not therapeutics. Key vitamins may help with those who have a specific need to maintain normal metabolic function – such as in the one-carbon methylation cycle which requires B vitamins for function. This does not suggest that these vitamins are therapeutic goods.

I hope these comment assist in you making a sensible decision,

s22 [redacted]

Response received 18/10/2019 1:49 pm s22

Dear s22

Please see correspondence attached.

Thank you, s22

s22

[redacted]

October 18, 2019

s22 [redacted]
[redacted]
Regulatory Compliance Section
Regulatory, Education and Compliance Branch

Dear s22 [redacted],

Thank you for your email of October 4 inviting comment on the proposed clarification that certain goods containing folate are therapeutic goods. I have been provided three key documents:

1) Complaint received from Dr Ken Harvey, Medreach Pty Ltd, along with some associated documents.
2) The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (2015)
3) The paper by Firth et al – The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials, World Psychiatry 2019; 18:308--324.

I have examined these documents in the context of considering whether a section 7 declaration is suitable for goods containing folate substances in certain circumstances. After considering these documents, the latter two of which I was already familiar with, I strongly retain my opinion that the proposed declaration is inappropriate. My reasons are as follows:

- The complaint from Dr Harvey is admirable in seeking to establish better regulations for medical foods/FSMPs. However, this does not reflect on whether any particular product is appropriately classed as a FSMP. Dr Harvey provides no evidence that Neurofolin should not be classed as a food, particularly as a FSMP. Therefore, in regard to the proposed section 7 declaration, Dr Harvey's letter also suggests that this is inappropriate as he

s22

[redacted]

believes Neurofolin to be ineffective as a therapeutic. Whether the concerns Dr Harvey raises around inappropriate marketing material are valid is something I am unable to comment on. However, I do strongly believe that the science currently supports trialling dietary management with patients diagnosed with treatment resistant (and other forms of) depression. The risk is negligible, and the cost is relatively minor. There is sufficient evidence that dietary management may be useful for a significant number of patients. Contrary to Dr Harvey's assertions, there is a considerable body of evidence finding a number of dietary-related deficiencies in patients diagnosed with major depressive disorder (MDD), folate levels being a key one. Given a FSMP is required to be taken under medical supervision, it is difficult to see how patients may mistakenly view or take a medical food as a therapeutic without this being corrected by the medical practitioner.

- I am familiar with the guidelines outlined in the second document. These guidelines are supportive of dietary enhancement using products containing folate substances. A FSMP like Neurofolin is the ideal product to trial such dietary enhancement. Declaring this range of products as therapeutics will directly conflict with these guidelines. For this additional reason I hope you decide against moving forward with the proposed section 7 declaration.
- The paper by Firth et al offers moderate support for the dietary enhancement described in the guidelines discussed above. At no point does it indicate that products containing only vitamins should be considered therapeutics. Therefore, I find nothing in this paper suggesting that a section 7 declaration is appropriate. On the contrary, it will only make it more difficult to attempt to help patients address dietary concerns related to their diseases.

s22

Depression is a common disorder that is managed at multiple levels in clinical practice. Refractory depression represents a considerable proportion of cases and psychiatrists often have to maneuver between both pharmacological and non-pharmacological interventions to treat the patients and avoid relapse- there is no simple algorithmic approach. For clinicians and patients to lose access to Neurofolin as a FSMP will limit the use of a safe and potentially beneficial option. I sincerely hope that the TGA will reconsider their current pathway and remove the proposed declaration from consideration.

Yours sincerely,

s22

s22

Response received 18/10/2019 3:50 pm s22

Dear s22,

Thank you for the invitation to comment on the additional documentation you provided on October 4, 2019. Please find attached my response.

Cheers

s22

Kind Regards

s22

e: s22 m: s22 LinkedIn: s22

w: s22

p: s22

s22

TGA Submission

Consultation: Proposed clarification that goods are therapeutic goods- goods containing folate substances in certain circumstances

I write in response to your invitation to comment on certain documents:

1. email sent by TGA 4/10/2019 containing documents
2. extension of deadline in email sent by TGA 9/10/2019
3. supplementary article forwarded by TGA on 15/10/2019.

Thank you for sending these documents and the opportunity to comment.

Should Foods with a Disease Modifying Effect Be Regulated As Therapeutic Goods?

The overarching issue appears to be that because a food may have a benefit for a disease state, should it be classified as a therapeutic good? We are used to seeing molecules and chemicals treated this way, and as the subject of research. We are now starting to see more food the subject of serious research - this does not make a food a therapeutic good.

There are many foods, or food components that may have a therapeutic benefit. The issue is not whether they do or don't, but *whether they are presented as having a therapeutic effect.* Foods that are presented as therapies should rightly be on the Australian Register of Therapeutic Goods (ARTG).

At Grunbiotics we have never intended to present our products as a substitute, alternative or equivalent to a therapeutic good. Grünbiotics was established with the express intention of entering the medical foods market, i.e. creating products that help manage the dietary aspects of a disease state. Or to put it another way, to create products that deal with the particular nutritional or dietary needs that accompany a disease.

Nothing in what you've sent changes my view that Neurofolin is a medical food.

Bias by Professor Harvey

Let me say at the outside that prior to this issue, and the documents you shared I had only a vague notion of Professor Ken Harvey. In preparing this submission I've had the opportunity to read more about Professor Harvey and The Friends of Science and Medicine (FSM). I have read some online articles, watched an Insight program on SBS on vitamins and supplements (https://www.sbs.com.au/ondemand/video/1448561731545) and read "Critical Discourse Analysis Of Rhetoric Against Complementary Medicine" (Flatt, 2013).

s22

Professor Ken Harvey appears to be a well-known and enthusiastic, albeit self-proclaimed *advocate for public health* https://www.linkedin.com/in/ken-harvey-326bab25/.

He is concerned about medicines and practices which are not as he claims, soundly grounded in science, and appears to particularly dislike Complementary and Alternative Medicines (CAM). (It is is somewhat surprising, then, to read in his complaint the allegation there is a regulatory double standard, that is "… unfair to the complementary medicine industry."). This is the same industry he alleges is "pseudo-science". Why Professor Harvey's sudden interest in defending the complementary medicine industry?

Unfortunately it appears that Professor Harvey fails to uphold the very scientific impartiality that he so cherishes. In the insight program mentioned above, he claims at one point that the TGA fails to examine 98% of its complaints. John Skerritt (the national manager of the TGA), rightly rebuffs this by explaining that complaints are triaged, and that in fact the vast majority of the *significant* complaints *are* investigated. This is just one example of Professor Harvey cherry-picking evidence to suit his agenda.

Other examples of inconsistencies are his submission of the paper "A Controlled Trial of Homocysteine Lowering and Cognitive Performance". This paper was published in 2006. Professor David Smith from Oxford University is a leader in this field. In a paper published in 2016, Smith makes the case for using B vitamins to lower homocysteine in order to prevent cognitive decline. There is a full 11 years between these papers - why would Professor Harvey choose an earlier paper by a lesser-known expert in the field? Why send the McMahon paper at all? Medical foods cannot claim a therapeutic benefit, so how is this relevant?

Professor Harvey has a number of objections to Neurofolin. These at times seems contradictory:

1. Professor Harvey argues there is " … insufficient evidence to support the use of L-methylfolate calcium for depression, either as adjunctive, or especially as sole therapy". Given that we are not trying to be a therapeutic good, this has little bearing or relevance.
2. I disagree with Ken Harveys assertion that there is no "good" evidence the management of the diet of patients with depression can be adequately achieved through normal diet. Plenty of evidence has been presented to the TGA to the contrary. In particular individuals with the MTHFR gene polymorphism have difficulty getting adequate folate from a normal diet.
3. It's interesting that Professor Harvey should use the term "good" evidence. Professor Harvey seems to choose evidence which supports his strongly stated points of view.

Professor Harvey's complaint about Neurofolin seems to be about the category, and issues between state food bodies, and the federal TGA. Neurofolin is in an example of the issues he raises - that is a broader conversation and declaring a section 7 for Neurofolin will not solve that issue.

Agreement with Professor Ken Harvey

Having said that, I wholeheartedly agree with some of Harvey's points:

1. The food-medicine interface is challenging. We attempted to follow it to the letter and yet inadvertently find ourselves on the wrong side of the TGA.
2. It would be better to have a single national body for food and therapeutic goods.
3. Sponsor self-determination will always have problems. As I may have said in my earlier submission, we did seek a number of occasions to get some clarification as to our product. It would have saved a lot of time and effort for all concerned if we had been able submit our product for approval – prior to spending millions of dollars and combined staff time of more than 12 years on its development.

Statements Not By Grünbiotics

Professor Harvey quotes a number of sources. I note that five of the eight sources he quotes from, are not owned or controlled by Grünbiotics. Grünbiotics should not be prosecuted for statements that other people make.

Terminololgy: "For The Dietary Management Of XZY" Or "For The Management Of The Diet Of People With XYZ"

I can't help but feel but that at the heart of our current discussion, is the terminology used in Food Standard 2.9.5. The standard states that an FSMP is for the "dietary management" of a disease state. To the layperson this could be interpreted as the disease can be managed through diet. What I believe the standard was intending to say is "for the management of the diet of people with XYZ disease state".

In our eagerness to meet standard 2.9.5 we thought it best to stick to the wording as closely as it was in the standard. In retrospect, it would have been better to use the longer, more cumbersome, but representive statement. Consider these in context:

- For the dietary management of depression = could be interpreted as implying that depression can you manage through diet.
- For the management of the diet of people with depression = helps people with depression manage their diet.

Many foods have a disease modifying effect - they should not be classified as therapeutic goods

Having said that, it should also be noted that many foods, and in fact diets have a disease modifying effect. It would be imprudent to classify them all therapeutic goods and, and would leave us very little to eat.

In the case of depression the recent SMILES sutdy carried out at Deakin University, Faculty of Health, School of Medicine showed many such links. In fact Deakin have established a whole centre simply looking at the link between food and mood: https://foodandmoodcentre.com.au/

Here are just a few papers which show how diet and nutrition can have a disease modifying effect:

- A modified Mediterranean dietary intervention for adults with major depression: dietary protocol and feasibility data from the SMILES trial.
  Opie, Rachelle S., O'Neil, Adrienne, Jacka, Felice N., Pizzinga, Josephine and Itsiopoulos, Catherine 2018. Nutritional neuroscience, vol. 21, no. 7, pp. 487-501, doi: 10.1080/1028415X.2017.1312841.
- Associations between fruit and vegetable consumption and depressive symptoms: evidence from a national Canadian longitudinal survey.
  M Kingsbury, G Dupuis, F Jacka, M Roy-Gagnon, S McMartin, I Colman (2016), Vol. 70, pp. 155-161, Journal of epidemiology and community health, London, Eng., C1.

Other examples include the use of trehalose - a simple sugar found in mushrooms - to deal with the damage caused by concussion (Lee, Yoon and Lee, 2018). Should mushrooms now be declared a therapeutic good? Most people would think that is ridiculous. There are plenty of other examples - olive oil may have a beneficial effect on dementia, pomegranate and Vitamin C for cancer.

We have at all times offered to work with the TGA to ensure that our products cannot be perceived as therapeutic goods. That offer still stands.

Neurofolin is Not a "try on"

In an email sent on 29 May 2018, the author makes a number of comments and assertions which I believe are incorrect:

1. There is no "stated dose". There is a "serve", and its nutritional components are contained in the Nutritional Information Panel (NIP). This is a FSANZ requirement. To allege that it is a "stated dose" is erroneous. How else can Grünbiotics meet the requirements of FSANZ? This is another example of Grunbiotics being caught

between a two regulatory authorities. If you can suggest another wording for this section Grünbiotics would happily change the wording to comply.

2. The email states that in the referenced paper L-methylfolate is not described as a food above. Whether or not the paper describes l-methylfolate as a food is beside the point. We are describing Neurofolin as a food, not one of its ingredients.
3. Finally this is not a "try-on". We did not raise millions of dollars from friends and family, and spend many years bringing this product to market as a "try-on". A simple conversation with us early on, would have made this very clear.

Summary

The broader regulatory issues, and disjuncture between various bodies (FSANZ, state food bodies and TGA) should be dealt with thoughtfully and thoroughly in a broader context. Grunbiotics and Neurofolin should not be the brunt such a resolution, or as you have stated "clarification". In any event, the proposed section 7 declaration creates more uncertainty then clarity.

Notwithstanding the strong complaint submitted by Professor Ken Harvey, and his considerable background and influence, nothing you have sent leads me to the conclusion that Neurofolin should be declared a therapeutic good. On the contrary, it points to Neurofolin being appropriate as a medical food. If there is any issue about is perception in the market, these can be addressed through changes to the marketing and packaging.

The proposed section 7 declaration is far too wide and will only serve to remove a beneficial product from the Australian market. It is yet another challenge, for people with an already challenging condition, to deal with. I urge you to reconsider. There are ways to deal with your concerns without the removal of this product from the market.

References

Flatt, J. (2013) *Critical Discourse Analysis of Rhetoric Against Complementary Medicine*. Available at: https://www.researchgate.net/publication/255972120.

Lee, H. J., Yoon, Y. S. and Lee, S. J. (2018) 'Mechanism of neuroprotection by trehalose: Controversy surrounding autophagy induction', *Cell Death and Disease*. Nature Publishing Group. doi: 10.1038/s41419-018-0749-9.

Smith, A. D. and Refsum, H. (2016) 'Homocysteine, B Vitamins, and Cognitive Impairment', *Annual Review of Nutrition*, 36(1), pp. 211–239. doi: 10.1146/annurev-nutr-071715-050947.

Response received 18/10/2019 4:38 pm s22

Dear s22,

Please find my attached response and comments on the documents I received from you on 4 October 2019, as part of the TGA's public consultation on a proposed declaration under s 7 of the Therapeutic Goods Act 1989.

Kind regards,

s22

s22

Find us on:

s22
Regulatory Compliance and Education Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dear s22

I am writing to provide comments on the documents I received from you on 4 October 2019 as part of the TGA's public consultation on a proposed declaration under s 7 of the *Therapeutic Goods Act 1989*. I am happy for my comments to be published on the TGA's website with my name and contact details (which are at the end of this letter) redacted.

These documents do not change my view that products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes. Studies suggest that insufficient folate and vitamin B12 status may contribute to major depressive disorder and that supplementation might be useful in this condition

People with depression are at high risk for early death, due to both a greater risk of suicide and the chronic diseases they experience. Thus, reducing the prevalence of depression would constitute a significant advancement in public health. Recent evidence suggests that depression may result, in some cases, from a nutritional deficiency, specifically iron deficiency. Iron deficiency is the most common of all nutritional deficiencies. It is estimated that as many as 70% of the world's population has inadequate iron status, and that 30% of the population has iron-deficiency anaemia. Iron deficiency is the only nutritional deficiency that is common in both developing and developed countries

However, recent evidence suggests that iron deficiency is also associated with depression, perhaps long before the routinely monitored clinical parameters indicate iron-deficiency anaemia. In some cases, individuals who have low iron status but are not sufficiently iron deficient to be anaemic (referred to as non-anaemic iron deficiency, NAID), show a much greater likelihood of being depressed than those with normal iron status.

Folic acid supplements play an important role in ensuring that vulnerable individuals and those in greater need of folate receive enough. Increasing intake of folate-rich foods is also important, as these foods typically also provide plenty of other nutrients that all act together to support good health.

Low folate status has been linked to an increased risk of depression and poor response to antidepressant treatment it has been suggested that supplementation of the nutrient could help treat low mood.

Folic acid supplementation has not been suggested as a treatment in itself for depression, but it may be helpful in improving response to antidepressants such as fluoxetine, and for these reasons I believe products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes.

RANZCP Guidelines

In relation to the RANZCP Guidelines, Table 17 on p 45 refers to 'Folate (including L-Methylfolate)' in a table headed 'Complementary therapies for depression'. The table entry states 'may assist depressive symptoms as adjunct to prescription medication'. Page 46 states 'several of the more commonly used complementary therapies used to assist mood are summarised in Table 17'.

I do not think that this reference to folate or L-methylfolate would mean that people in the community are more likely to interpret Neurofolin as being a substitute for prescription medicine. To my mind, the use of the word 'therapy' does not change the fact that the RANZCP Guidelines make clear that folate or L-Methylfolate may be used in conjunction with treatments that have therapeutic value. Folate or L-methylfolate may be used to support such treatments, but I do not interpret the RANZCP Guidelines as suggesting that it is a treatment in its own right. I do not think anything contained in the RANZCP Guidelines provides a robust argument against the correct classification of Neurofolin as a Food for Special Medical Purposes.

Firth et al, *Efficacy and safety of nutrient supplements*

The Firth article's overarching conclusion is that there is a strong relationship between nutrition and mental disorders and there is a growing acknowledgement of this relationship within the community. This article also sets outs the results of a number of clinical trials that examine the effects of a high dose of methylfolate as an adjunctive treatment for mental disorders and concludes that there are benefits for depressive symptoms. Within the context of this paper's discussion of nutrition and its benefits and the clear lack of detrimental side effects of methylfolate this does not suggest a therapeutic mechanism of action.

Complaint dated 29 May 2018

This document sets out some details about Neurofolin and refers to a referenced paper and continues that the paper's 'description of the action of L-Methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food'.

I do not agree with this statement. Even if the paper attached to the complaint does not describe L-methylfolate using the word 'food', it describes it as a 'derivative of the vitamin folate'. In my view vitamins are one of the key components of foods, and folate is found in many everyday foods.

Every nutrient in food can be shown to have some kind of effect at a physiological level; e.g. Vitamin C or water.

Complaint from Dr Ken Harvey dated 19 May 2019

This complaint does not change my view that Neurofolin should be available for sale as a FSMP and I would make the following observations about this document:

- it appears to be a broader complaint about products in the FSMP category and targets Neurofolin as just one of a number of examples;
- it states that there is insufficient evidence that L-methylfolate is an adjunctive or sole therapy for depression, however this does not appear to be consistent with the RANZCP Guidelines or the Firth article provided;
- it lists a number of claims about Neurofolin as being 'misleading or deceptive' but having read those claims I do not agree with this statement;
- it says that consumers with depression do not have a medically determined nutrient requirement for L-Methylfolate, however my understanding is that there is evidence that depression and low folate levels are linked in many patients;
- it quotes an incorrect reference to the relevant "Food for Special Medical purposes" standard in the Food Standards Code.

Controlled trial of homocysteine lowering and cognition

This document does not seem particularly relevant to the current consultation. It provides no robust evidence of the use, or likely use, of folate as a therapeutic treatment. This document does not alter my opinion that Neurofolin is correctly characterised as an FSMP.

This is a lengthy document and I am making these comments in general but have not been given particular parts about which the TGA is seeking my views. I would be able to provide more specific comments if provided with particular references.

Yours faithfully

s22

PKU air® + OMEGA 3

Description
A food for special medical purposes.
PKU air® is a ready-to-drink, phenylalanine free protein substitute, containing essential and non-essential amino acids, carbohydrate, vitamins, minerals, trace elements and the omega-3 long chain polyunsaturated fatty acids (LCPs); docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). With sugar and sweeteners.
Available in a choice of flavours.

Indications
PKU air is for use in the dietary management of Phenylketonuria (PKU) from 3 years onwards.

Dosage and Administration
To be determined by the clinician or dietitian, and is dependent on the age, body weight and medical condition of the patient.

PKU air15 (130ml) = 15g PE	PKU air20 (174ml) = 20g PE

The product can be used individually or interchanged to meet individual protein requirements.
1. The daily protein substitute requirement is given as PKU air.
2. Additional protein is provided from exchanges of natural protein, to provide phenylalanine in controlled amounts, which is essential for growth and development.
3. Foods high in carbohydrate and fat, but low in protein, should be provided to supply the remainder of the energy.

Preparation Guidelines

Shake well | Open | Drink

Water or permitted drinks should be taken after PKU air.

IMPORTANT NOTICE

Must only be given to patients with proven PKU under strict medical supervision.

Suitable from 3 years onwards.

Diet must be supplemented with natural protein, water and other nutrients in prescribed quantities to supply phenylalanine, fluid and general nutritional requirements.

Not for use as a sole source of nutrition.

For enteral use only.

PKU

Nutritional Information

		Per 100ml	Per PKU air15 130ml	Per PKU air20 174ml
Energy	kJ	243	316	423
	kcal	57	75	100
Fat	g	0.6	0.8	1.0
of which saturates	g	0.1	0.1	0.2
Carbohydrate	g	1.5	2.0	2.6
of which sugars	g	0.1	0.1	0.2
Protein equivalent	g	11.5	15	20
L-Phenylalanine	g	0	0	0
Salt	g	0.25	0.32	0.43
Vitamins and minerals				
Vitamin A (RE)	µg	160	208	278
Vitamin E (aTE)	mg	3.0	3.9	5.2
Vitamin D	µg	5.8	7.5	10
Vitamin K	µg	19	25	33
Vitamin C	mg	21	27	37
Thiamin	mg	0.40	0.52	0.70
Riboflavin	mg	0.44	0.57	0.77
Vitamin B6	mg	0.46	0.60	0.80
Niacin mg (mg NE)		4.8 (9.6)	6.2 (13)	8.4 (17)
Folic acid	µg	77	100	134
Vitamin B12	µg	0.92	1.2	1.6
Pantothenic Acid	mg	1.5	2.0	2.6
Biotin	µg	36	47	63
Sodium	mg	98	127	171
	mmol	4.2	5.5	7.3
Chloride	mg	140	182	244
	mmol	3.9	5.1	6.8
Potassium	mg	180	234	313
	mmol	4.5	5.9	7.8
Calcium	mg	230	299	400
	mmol	5.8	7.5	10
Phosphorus	mg	210	273	365
Phosphate	mmol	6.7	8.7	12
Magnesium	mg	72	94	126
	mmol	3.0	3.9	5.2
Iron	mg	4.2	5.5	7.3
Zinc	mg	4.2	5.5	7.3
Copper	mg	0.42	0.55	0.73
Iodine	µg	49	64	85
Selenium	µg	17	22	30
Manganese	mg	0.60	0.78	1.0
Chromium	µg	17	22	30
Molybdenum	µg	28	36	48

Nutritional information

		Per 100ml	Per PKU air15 130ml	Per PKU air20 174ml
Others				
Choline	mg	110	143	191
DHA	mg	77	100	134
EPA	mg	18	23	31
Amino Acids				
L-Alanine	g	0.53	0.69	0.92
L-Arginine	g	0.86	1.12	1.50
L-Aspartic Acid	g	1.36	1.77	2.37
L-Cystine	g	0.35	0.46	0.61
L-Glutamine	g	0	0	0
Glycine	g	1.35	1.76	2.35
L-Histidine	g	0.53	0.69	0.92
L-Isoleucine	g	0.93	1.21	1.62
L-Leucine	g	1.46	1.90	2.54
L-Lysine	g	0.96	1.25	1.67
L-Methionine	g	0.26	0.34	0.45
L-Proline	g	0.97	1.26	1.69
L-Serine	g	0.60	0.78	1.04
L-Threonine	g	0.93	1.21	1.62
L-Tryptophan	g	0.29	0.38	0.50
L-Tyrosine	g	1.37	1.78	2.38
L-Valine	g	1.07	1.39	1.86
L-Carnitine	mg	13	17	23
Taurine	mg	25	33	44

Osmolality:
PKU air green: 1375mOsm/kg **PKU air gold:** 1425mOsm/kg
PKU air red: 1491mOsm/kg **PKU air white:** 1485mOsm/kg

Allergen Declaration
Contains fish (tuna oil)
Contains soya (soya lecithin)
Contains milk (milk protein)

Pack Size/Weight

•air15
30 x 130ml pouches = 3.9L

•air20
30 x 174ml pouches = 5.22L

Flavours
Green* (citrus twist),
gold* (coffee fusion), red (berry blast)
and white (caribbean crush)

Storage
Store in a cool, dry place.
Once opened drink immediately or recap, refrigerate and use within 24 hours.

Response received 18/10/2019 5:52 pm

s22 [redacted]

Dear s22 [redacted],

I am writing to provide comments on the documents I received from you on October 4 2019 as part of the TGA's public consultation on a proposed declaration under s 7 of the Therapeutic Goods Act 1989.

These documents do not change my view that products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes.

RANZCP Guidelines

In relation to the RANZCP Guidelines, Table 17 on p 45 refers to 'Folate (including L-Methylfolate)' in a table headed 'Complementary therapies for depression'. The table entry states 'may assist depressive symptoms as adjunct to prescription medication'. Page 46 states 'several of the more commonly used complementary therapies used to assist mood are summarised in Table 17'.

I do not think that this reference to folate or L-methylfolate would mean that people in the community are more likely to interpret Neurofolin as being a substitute for prescription medicine. To my mind, the use of the word 'therapy' does not change the fact that the RANZCP Guidelines make clear that folate or L-Methylfolate may be used in conjunction with treatments that have therapeutic value. Folate or L-methylfolate may be used to support such treatments, but I do not interpret the RANZCP Guidelines as suggesting that it is a treatment in its own right. I do not think anything contained in the RANZCP Guidelines provides a robust argument against the correct classification of Neurofolin as a Food for Special Medical Purposes.

Firth et al, Efficacy and safety of nutrient supplements

The Firth article's overarching conclusion is that there is a strong relationship between nutrition and mental disorders and there is a growing acknowledgement of this relationship within the community. This article also sets outs the results of a number of clinical trials that examine the effects of a high dose of methylfolate as an adjunctive treatment for mental disorders and concludes that there are benefits for depressive symptoms. Within the context of this paper's discussion of nutrition and its benefits and the clear lack of detrimental side effects of methylfolate this does not suggest a therapeutic mechanism of action.

Complaint dated 29 May 2018

This document sets out some details about Neurofolin and refers to a referenced paper, and continues that the paper's 'description of the action of L-Methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food'.

I do not agree with this statement. Even if the paper attached to the complaint does not describe L-methylfolate using the word 'food', it describes it as a 'derivative of the vitamin folate'. In my view vitamins are one of the key components of foods, and folate is found in many everyday foods.

Every nutrient in food can be shown to have some kind of effect at a physiological level; e.g. Vitamin C or water.

Complaint from Dr Ken Harvey dated 19 May 2019

This complaint does not change my view that Neurofolin should be available for sale as a FSMP and I would make the following observations about this document:

- it appears to be a broader complaint about products in the FSMP category and targets Neurofolin as just one of a number of examples;
- it states that there is insufficient evidence that L-methylfolate is an adjunctive or sole therapy for depression, however this does not appear to be consistent with the RANZCP Guidelines or the Firth article provided;
- it lists a number of claims about Neurofolin as being 'misleading or deceptive' but having read those claims I do not agree with this statement;
- it says that consumers with depression do not have a medically determined nutrient requirement for L-Methylfolate, however my understanding is that there is evidence that depression and low folate levels are linked in many patients;
- it quotes an incorrect reference to the relevant "Food for Special Medical purposes" standard in the Food Standards Code.

This is a lengthy document and I am making these comments in general but have not been given particular parts about which the TGA is seeking my views. I would be able to provide more specific comments if provided with particular references.

Regards

s22 [redacted]

Response received 18/10/2019 6:05 pm [redacted]

Dear [redacted],

Please find my attached response and comments on the documents I received from you on 4 October 2019, as part of the TGA's public consultation on a proposed declaration under s 7 of the *Therapeutic Goods Act 1989*.

Regards,

[redacted]

[redacted]

s22
Regulatory Compliance and Education Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dear s22

I am writing to provide comments on the documents I received from you on 4 October 2019 as part of the TGA's public consultation on a proposed declaration under s 7 of the *Therapeutic Goods Act 1989*. I am happy for my comments to be published on the TGA's website with my name and contact details (which are at the end of this letter) redacted.

These documents do not change my view that products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes. Studies suggest that insufficient folate and vitamin B12 status may contribute to major depressive disorder and that supplementation might be useful in this condition

People with depression are at high risk for early death, due to both a greater risk of suicide and the chronic diseases they experience. Thus, reducing the prevalence of depression would constitute a significant advancement in public health. Recent evidence suggests that depression may result, in some cases, from a nutritional deficiency, specifically iron deficiency. Iron deficiency is the most common of all nutritional deficiencies. It is estimated that as many as 70% of the world's population has inadequate iron status and that 30% of the population has iron-deficiency anaemia. Iron deficiency is the only nutritional deficiency that is common in both developing and developed countries

However, recent evidence suggests that iron deficiency is also associated with depression, perhaps long before the routinely monitored clinical parameters indicate iron-deficiency anaemia. In some cases, individuals who have low iron status but are not sufficiently iron deficient to be anaemic (referred to as non-anaemic iron deficiency, NAID), show a much greater likelihood of being depressed than those with normal iron status.

Folic acid supplements play an important role in ensuring that vulnerable individuals and those in greater need of folate receive enough. Increasing intake of folate-rich foods is also important, as these foods typically also provide plenty of other nutrients that all act together to support good health.

Low folate status has been linked to an increased risk of depression and poor response to antidepressant treatment it has been suggested that supplementation of the nutrient could help treat low mood.

Folic acid supplementation has not been suggested as a treatment in itself for depression, but it may be helpful in improving response to antidepressants such as fluoxetine, and for these reasons, I believe products like Neurofolin should be available for Australians who need them as Foods for Special Medical purposes.

RANZCP Guidelines

In relation to the RANZCP Guidelines, Table 17 on p 45 refers to 'Folate (including L-Methylfolate)' in a table headed 'Complementary therapies for depression'. The table entry states 'may assist depressive symptoms as an adjunct to prescription medication'. Page 46 states 'several of the more commonly used complementary therapies used to assist mood are summarised in Table 17'.

I do not think that this reference to folate or L-methylfolate would mean that people in the community are more likely to interpret Neurofolin as being a substitute for prescription medicine. To my mind, the use of the word 'therapy' does not change the fact that the RANZCP Guidelines make clear that folate or L-Methylfolate may be used in conjunction with treatments that have therapeutic value. Folate or L-methylfolate may be used to support such treatments, but I do not interpret the RANZCP Guidelines as suggesting that it is a treatment in its own right. I do not think anything contained in the RANZCP Guidelines provides a robust argument against the correct classification of Neurofolin as a Food for Special Medical Purposes.

Firth et al, *Efficacy and safety of nutrient supplements*

The Firth article's overarching conclusion is that there is a strong relationship between nutrition and mental disorders, and there is a growing acknowledgement of this relationship within the community. This article also sets outs the results of several clinical trials that examine the effects of a high dose of methylfolate as an adjunctive treatment for mental disorders and concludes that there are benefits for depressive symptoms. Within the context of this paper's discussion of nutrition and its benefits and the clear lack of detrimental side effects of methylfolate this does not suggest a therapeutic mechanism of action.

Complaint dated 29 May 2018

This document sets out some details about Neurofolin and refers to a referenced paper and continues that the paper's 'description of the action of L-Methylfolate has all the attributes of a pharmacological effect and nowhere in the paper is it described as a food'.

I do not agree with this statement. Even if the paper attached to the complaint does not describe L-methylfolate using the word 'food', it describes it as a 'derivative of the vitamin folate'. In my view vitamins are one of the key components of foods, and folate is found in many everyday foods.

Every nutrient in food can be shown to have some kind of effect at a physiological level; e.g. Vitamin C or water.

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This complaint does not change my view that Neurofolin should be available for sale as a FSMP and I would make the following observations about this document:

- it appears to be a broader complaint about products in the FSMP category and targets Neurofolin as just one of several examples;
- it states that there is insufficient evidence that L-methylfolate is an adjunctive or sole therapy for depression, however this does not appear to be consistent with the RANZCP Guidelines or the Firth article provided;
- it lists several claims about Neurofolin as being 'misleading or deceptive' but having read those claims I do not agree with this statement;
- it says that consumers with depression do not have a medically determined nutrient requirement for L-Methylfolate; however my understanding is that there is evidence that depression and low folate levels are linked in many patients;
- it quotes an incorrect reference to the relevant "Food for Special Medical purposes" standard in the Food Standards Code.

Controlled trial of homocysteine lowering and cognition

This document does not seem particularly relevant to the current consultation. It provides no robust evidence of the use, or likely use, of folate as a therapeutic treatment. This document does not alter my opinion that Neurofolin is correctly characterised as an FSMP.

This is a lengthy document, and I am making these comments in general but have not been given particular parts about which the TGA is seeking my views. I would be able to provide more specific comments if provided with particular references.

Yours faithfully

s22

Response received 21/10/2019 5:37 pm

s22 [redacted]

Dear s22 [redacted],

Thank you for your request for further comment on the consultation on the proposed clarification that goods containing folate substances in certain circumstances are therapeutic goods.

The team at s22 [redacted] have not had the opportunity to review the articles sent during the last few weeks and are not able to provide further comments at present. If the deadline for comments can be extended further (to 25-Oct-2019?), s22 [redacted] may be able to provide further comments.

Kind regards,

s22 [redacted]

Response received 23/10/2019 5:11 pm s22

Dear s22,

Thank you for the extension to review the additional pieces of information provided.

These information illustrate that "folate" and "folate-based" substances have a legitimate therapeutic use, as is the case with many vitamins, minerals, and essential nutrients. It does not however change s22's position that the current regimes are adequate or outweigh its concerns that, in view of legitimate non-therapeutic (including FSMPs) uses for "folate" and "folate-based" substances, the declaration proposed by the TGA appears to single out folate from other permitted forms of substances that may be added to FSMPs.

Therefore,

- s22's position remains that the proposed declaration should not be made for the reasons previously submitted however is supportive of all measures to ensure that therapeutic goods and FSMPs are appropriately regulated, supplied and advertised to consumers.

- s22 notes the TGA's response to the Complaint in the document entitled "FOI request concerning previous complaint about Neurofolin" that "there is an open case being managed by the Regulatory Compliance Section (RCS)."

- This supports s22 position comment 2, that the TGA is already empowered to act on a **case-by-case basis in the event of that a food (or food for special medical purpose, FSMP) is advertised as therapeutic goods or non-compliant goods and evidences that the TGA does effectively exercise its powers to do so.**

- **A similar regulatory approach to folate/folate based substance(s) is adopted by the European Food Safety Authority (EFSA) and Food & Drug Administration (see links below)**

o **https://www.nutraingredients.com/Article/2006/03/09/Merck-s-Metafolin-receives-EU-approval**

o **https://www.foodstandards.gov.au/code/applications/documents/A566%20L-Methylfolate%20FAR%20FINAL.pdf**

o **https://www.deplin.com/pdf/DEPLINCapsulesPIStatement.pdf**

Kind regards,

s22

Response received 18/10/2019 11:39 pm [redacted]

Dear [redacted],

I have only just been made aware of this submission and therefore adequate time to respond to the claims made in the initial complaint is a difficult task the night before submissions close.

I have been a registered pharmacist for 13 years and now soon to become a junior doctor.

Neurofolin is an effective product with no known adverse effects or drug interactions.

The claims made in the complaints submission are incorrect and extraordinary that they have been made, such as:

1. I could not find evidence that showed L-methylfolate is "deficient in individuals with depressive disorders" nor that it "helps nutritionally support mood regulation".

This statement is extraordinary in that it is well established in psychiatry that, 'abnormal folate metabolism has long been associated with mood disorders' Theodore A. Stern, et al - Massachusetts General Hospital Comprehensive Clinical Psychiatry-Elsevier (2015)

Further to this the study carried out by Papakostas et al. was robust in its design, statically significant and has been replicated.

L-Methyfolate is safe, extremely well tolerated and has no known side effects reported.

In my role as a pharmacist I have recommended Neurofolin as both augmentation therapy with SSRI's and SNRI's with great success and have had direct phone calls from general practitioners and psychiatrists congratulating my intervention impressed with its efficacy I often receive Neurofolin written down as therapy for patients.

Additionally to recommending Neurofolin and having at least 50 regular patients who are compliant with therapy and actively return for a resupply each month I personally have used nerufolin for over a year. The benefits are truly remarkable. My response is not hyperbole but rather the correct adjective, the response in terms of mood, energy, affect and motivation is remarkable.

I have not experienced any adverse effects, nor have any of my patients reported any negative effects, on the contrary for a relatively expensive product not PBS listed low-income earners and commonwealth supported people return regularly for a resupply and occasionally further counselling.

My response is an anecdotal response that if required could form a controlled study which I am confident based on strong clinical practice replicate the findings of its initial positive effects on depression as monotherapy or in augmentation of antidepressants.

Regardless of the purported lack of efficacy or its claim to be rescheduled, Neurofolin is a neutraceutical, a safe and effective treatment for depression that is adverse effect and risk free. A great deal of patients suffering with depression have been given access to a safe, effective and interaction free nutraceutical that is sold in pharmacy by a registered Pharmacist. A pharmacist is a health care professional with expertise in medication therapy and management and therefore restricting access to this safe and effective product that is sold by the most qualified health professional to be doing would be catastrophic to those patients that rely on this safe and effective means of depression management.

I therefore beseech you to confirm that Neurofolin consider as requested to confirm to the complitant that this is an appropriate 'food for special medicinal purposes".

This is a truely disturbing submission that would not serve the community but rather deprive suffering patients of safe, effective, adverse effect and interaction free therapy.

Sincerely

s22 [redacted]