Submission for Folic Acid

Part A
1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Folic acid (including folate and folacin).

2. Proprietary name(s).

Not applicable.

3. Name of the company / organisation / individual requesting a reclassification.

Not applicable. This request is made on behalf of the natural health products industry.

4. Dose form(s) and strength(s) for which a change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

5. Pack size and other qualifications.

Not applicable. This request is made on behalf of the natural health products industry.

6. Indications for which change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

7. Present classification of the medicine.

The present classification for folic acid also covers the following substances:

- (6S)-5-Methyltetrahydrofolic acid, glucosamine salt
- Calcium L-5-methyltetrahydrofolate
- Levomefolic acid (folinic acid).

At the present time, folic acid is:

- Unscheduled when in products for oral use, below 300 µg.
- Unscheduled when in products for oral use, between 300 and 500 µg provided the manufacture is performed according to the Code of Good Manufacturing Practice for medicines.
- Unscheduled when in parenteral nutrition replacement preparations.
- Pharmacy-only medicine when the Recommended Daily Dose (RDD) exceeds 500 µg.
- Prescription medicine when for injection, except in parenteral nutrition replacement preparations.

8. Classification sought.

It is proposed that folic acid is scheduled as:

- Pharmacy-only medicine when the Recommended Daily Dose (RDD) exceeds 1000 µg.
- Prescription medicine when for injection, except in parenteral nutrition replacement preparations.

It should be noted that natural health products are to be required to be manufactured according to a Code of Manufacturing Practice. This will include NHPs containing folic acid at 1000 µg if the proposed change is accepted.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia
Unscheduled below 500 µg.
Pharmacy medicine in preparations containing more than 500 µg of folic acid per recommended daily dose.
Prescription only medicine in preparations for human use for injection.

Canada
Unscheduled at 1000 µg and below.
Prescription drug in oral dosage form containing more than 1.0 mg of folic acid per dosage form or, where the largest RDD shown on the label would, if consumed by a person, result in the daily intake by that person of more than 1.0 mg of folic acid.

UK
Prescription medicine in preparations containing more than 500 µg of folic acid per recommended daily dose.

Folic acid recommendations internationally
In 2015 a study was published on the recommended folate and folic acid intakes prior to conception in 36 countries. In this study it was concluded that the most common recommendation for folic acid supplementation prior to conception is 400 µg per day. For women of childbearing age the general recommendation was in the range of 300 to 400 µg per day and for pregnant woman it was in the range of 500 to 600 µg per day. The researchers noted that there were big differences observed in the recommendation of some countries (Gomes, Lopes & Pinto, 2015).

Many countries, including the United States and Canada, have mandatory fortification of flour with folic acid and two thirds of the world's population has access to folic acid-fortified flour. In Australia, the government has mandated folic acid fortification of wheat flour for bread-making purposes.

In New Zealand, a proposal for mandatory fortification of folic acid in bread at a level of 80-180 µg per 100 grams of bread (about 3 to 4 slices) was deferred in favour of voluntary fortification. Some manufacturers also voluntarily choose to fortify other foods with folic acid eg breakfast cereal, some fruit juices, some pasta and meat products.

10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.

Folic acid is commonly available in dietary supplement tablets at 300 µg, and in some medicines at 500 µg. It is also present in fortified foods at lower levels.

Products containing folic acid above 500 µg are scheduled medicines required to meet the Code of Good Manufacturing Practice for the Manufacture and Distribution of Therapeutic Goods.

When the NHP Bill is passed, natural health products containing folic acid up to 500 µg will have to meet a Code of Manufacturing Practice for natural health products. In addition, it is proposed that dose form that are a chewable, effervescent, dispersible or modified release tablet, or a soft or modified release capsule, will be required to meet USP requirements for products containing folic acid.

11. Labelling or draft labelling for the proposed new presentation(s).

In a consultation draft version of the Permitted Substances List for natural health products, the following statements are currently proposed for natural health products containing folic acid:

> *Vitamins can only be of assistance if the dietary vitamin intake is inadequate*
> [or]
> *Vitamin supplements should not replace a balanced diet.*

These same statements are required on the labels of Listed Medicines containing folic acid in Australia.

12. Proposed warning statements if applicable.

In Canada, the following statements are required on products with a daily dose of 200-399 µg folic acid:

> Folate supplementation can mask a vitamin B12 deficiency. If you are unsure whether you are taking enough vitamin B12, consult a health care practitioner prior to use.

The New Zealand Food Safety Authority reported that UK and Australia has noted that high levels of folic acid could interfere with certain drugs which affect folate metabolism, such as anticonvulsants (New Zealand Food Safety Authority, 2004).

It is proposed that these risks could be mitigated by including a label advisory statement to the effect:

> *Folate supplementation can mask a vitamin B12 deficiency or interfere with medicines that affect folate metabolism. Consult a health care practitioner prior to use.*

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

If this submission is accepted, current approved medicines that will be affected are:

Apo-Folic tablets	800 µg	(Apotex)
Cernevit powder for injection	414 µg	(Baxter)
Elevit tablets	800 µg	(Bayer)
Elevit with Iodine tablets	800 µg	(Bayer)
Ferro-F tablets	350 µg	(AFT Pharmaceuticals)
Ferrograd F	350 µg	(BGP Products)
Menevit capsules	500 µg	(Bayer)
Nutriway Vitamin B Complex tablets	130 µg	(Amway of New Zealand)
Soluvit N powder for injection	400 µg	(Fresenius Kabi)

Manufacturers of these medicines may choose to increase the folic acid content to 1000 µg.

Some manufacturers of medicines may choose to re-position their medicines as natural health products regulated under the NHP Act if the quantity of folic acid is the only parameter preventing this from currently happening.

Manufacturers of current dietary supplement-type products will likely increase the quantity of folic acid in their products. It should be noted that all dietary supplement products will be regulated under the NHP Bill.

Part B Reasons for requesting classification change including benefit-risk analysis.

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand's recommended intakes for folic acid are:

Age group and gender		Folate as dietary folate equivalents µg / day		
		EAR	RDI	UL
Children	1-3 years	120	150	300
	4-8 years	160	200	400
Boys	9-13 years	250	300	600
	14-18 years	330	400	800
Girls	9-13 years	250	300	600
	14-18 years	330	400	800
Men	19-30 years	320	400	1,000
	31-50 years	320	400	1,000
	51-70 years	320	400	1,000
	> 70 years	320	400	1,000
Women	19-30 years	320	400	1,000
	31-50 years	320	400	1,000
	51-70 years	320	400	1,000
	> 70 years	320	400	1,000
Pregnancy	14-18 years	520	600	800
	19-30 years	520	600	1,000
	31-50 years	520	600	1,000
Lactation	14-18 years	450	500	800
	19-30 years	450	500	1,000
	31-50 years	450	500	1,000

EAR estimated average requirement
RDI recommended daily intake
UL upper level of intake

The Ministry of Health recommends that women contemplating pregnancy (who are at low risk of a neural tube defect affected pregnancy) take 800 µg of folic acid daily for at least four weeks prior to conception and continuing for 12 weeks after conception. This RDD is increased to 5 mg of folic acid for women who are at high risk of an affected pregnancy. A 5 mg dose is also recommended or women who are on insulin treatment for diabetes, are taking medications known to affect folate metabolism such as anti-convulsants, infertility treatment, vitamin A analogues used to treat acne and some anti-tumor agents; for example, carbemazepine, clomiphene, valproate, retinoids and etretinate. This should be taken for at least four weeks prior to conception and for 12 weeks after conception to reduce the risk of NTDs (Ministry of Health, 2016).

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim to treat the common cold with zinc tablets could be allowed if there was sufficient evidence. The benefits of folic acid in the prevention or treatment of a number of physiological conditions are well established.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

In 2004 the New Zealand Food Safety Authority (NZFSA – now Ministry for Primary Industries, MPI) released a public discussion paper proposing changes to the Dietary Supplements Regulations 1985 (New Zealand Food Safety Authority, 2004).

In countries where the average diet contains foliate, the recommended daily dose of folate is around 400 µg (cf the current 300 µg / 500 µg split in New Zealand between dietary supplements and medicines). It was estimated in 2004 that the average person in New Zealand had a usual daily intake of around 300 µg so a supplementation at 500 µg was considered necessary to reach the 800 µg needed to prevent neural tube defects during pregnancy.

In their discussion paper NZFSA proposed to change the permitted levels of folic acid from 300 to 500 µg and provided a risk assessment of folic acid. In the risk assessment it was noted that according to the USA, UK and Australia, folic acid is generally considered safe, and that an upper limit of 1000 µg a day was not expected to result in any adverse effects.

Orally, folic acid is considered to be well tolerated in amounts found in fortified foods and supplements in doses less than 1000 µg per day (Food and Nutrition Board, Institute of Medicine, 2000)

The potential for harm arises where a person already on an average diet (300 µg) also supplements with products containing up to 1000 µg folic acid.

The United States and UK have both established upper limits for folic acid at 1000 µg per day. The limits are slightly different, in that:

- the United States upper limit relates to folic acid from fortified foods and supplements (ie synthetic folic acid) and is exclusive of food folate (IOM, 1998); whereas
- the UK upper limit is a guidance level only. The upper limit of 1000 µg per day relates to a supplemental dose, and is exclusive of both food folate and folic acid added to fortified foods (UK FSA, 2003).

Excessive folate

The National Institutes of Health report that some population groups are at risk of obtaining excessive folate. People aged 50 years and older have the highest total folate intakes and about 5% have intakes exceeding the UL of 1,000 µg per day, primarily due to folic acid from dietary supplements (Bailey RL, Dodd et al 2010a).

Many children's intakes also exceed the UL. When folic acid from both food and dietary supplements is considered, 30% to 66% of children aged 1 to 13 years have intakes exceeding the UL of 300–600 µg per day depending on age (Bailey RL, Dodd et al 2010b). Almost all children aged 1 to 8 years who consume at least 200 µg /day folic acid from dietary supplements have total folate intakes that exceed the UL (Yeung et al, 2011). However, it is not clear whether this is of concern because little is known about the long-term effects of high folic acid doses in children (Yetley et al, 2011).

Cognition and Vitamin B12 deficiency

There is some concern that consuming high amounts of folic acid from the diet and/or supplements might worsen cognitive decline in older people. A large-scale study suggests that people over 65 years of age, who consume large amounts of folic acid (median of 742 µg /day), have cognitive decline at a rate twice as fast as those consuming smaller amounts (median of 186 µg /day). It is not known if this is directly attributable to folic acid. It is theorised that this could be due to folic acid masking a vitamin B12 deficiency. Vitamin B12 deficiency is associated with cognitive decline (Morris et al, 2005).

Large doses of folic acid can also precipitate or exacerbate neuropathy in people deficient in vitamin B12 (Food and Nutrition Board, Institute of Medicine, 2000). Large amounts of folic acid can correct the megaloblastic anaemia, but not the neurological damage, that can result from vitamin B12 deficiency. Some experts have therefore been concerned that high folic acid intakes might "mask" vitamin B12 deficiency until its neurological consequences become irreversible. But anaemia is no longer the basis for diagnosing vitamin B12 deficiency, so the focus of concern has shifted to the possibility that large amounts of folic acid could precipitate or exacerbate the anaemia and cognitive symptoms associated with vitamin B12 deficiency, perhaps by increasing homocysteine or methylmalonic acid concentrations (Institute of Medicine. Food and Nutrition Board, 1998; Clarke et al, 2010; Johnson, 2007; Morris et al, 2007; Selhub et al, 2007, Selhub et al, 2009).

However, the high homocysteine and methylmalonic acid concentrations in people with both low vitamin B12 and high folate concentrations could be due to severe malabsorptive conditions or pernicious anemia rather than high folic acid intakes (Berry et al, 2007; Carmel 2009). High blood folate concentrations do not appear to exacerbate vitamin B12 deficiency in healthy, young adults (Mills et al, 2011)

Health Canada manages possible risk by requiring the warning statement:

> Folate supplementation can mask a vitamin B12 deficiency. If you are unsure whether you are taking enough vitamin B12, consult a health care practitioner prior to use.

Cancer

There has been some concern that high dose folic acid might increase the risk of adverse cardiovascular outcomes and cancer. However, the European Food Safety Authority convened a meeting of experts to consider the evidence on the possible relationship regarding folic acid and risk of cancer. The meeting identified key knowledge gaps and made a number of research recommendations. It considered the results of randomised control trials (RCTs) designed to test the effect of folic acid on recurrence of colorectal adenomas. These studies produced different results: four studies with 3 year interventions reported no

adverse effects, whereas one longer term study reported adverse effects on adenomas in the intervention group. The meeting also considered evidence on cancer occurrence collected from participants in a consortium of RCTs designed to test the hypothesis that folic acid and other B vitamins would reduce CVD risk. The totality of evidence from the meta-analysis of these CVD trials does not suggest that folic acid is associated with increased cancer risk. The EFSA added that the meta-analysis probably did not have sufficient power to detect over all or site specific cancer risk (EFSA 2009).

Comment
The main concerns from excessive folate intake is that it may mask Vitamin B12 deficiency and a link to cancer has been suspected. These do not appear to be supported by the reported studies and reviews. Assuming that the average dietary intake of folic acid is 300 µg, supplementation with an additional 1000 µg would bring total folic acid intake to 1300 µg a day. Evidence indicates that daily supplementation of folic acid as high as 5-15 mg is safe (Crayhon, 2001). Nevertheless, if it is considered necessary in order to allow an increase in the limit for folic acid to 1000 µg/day, it is proposed that any potential risk can be mitigated by including a label advisory statement to the effect:

> *Folate supplementation can mask a vitamin B12 deficiency or interfere with medicines that affect folate metabolism. Consult a health care practitioner prior to use.*

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Not applicable.

4. Relevant comparative data for like compounds.

Not applicable.

5. Local data or special considerations relating to New Zealand.

The Ministry of Health reported in 2003 (MOH, 2016) that neural tube defects were the highest in early pregnancy terminations (5.7 cases per 10,000 total births), followed by live births (3.4 per 10,000) and foetal deaths (2.1 per 10,000).

At the present time the Medicines Schedule entry for folic acid is harmonised with Australia. An increase in the allowed limit to 1000 µg will de-harmonise the Medicines Schedule with Australia. However, it will harmonise with the allowed limit in Canada for folic acid in natural health products.

6. Interactions with other medicines.

The UK and Australia noted that high levels of folic acid could interfere with certain drugs which affect folate metabolism, such as anticonvulsants (New Zealand Food Safety Authority, 2004). This was also noted in the Data Sheets for Calcium Folinate Ebewe, DBL™ Leucovorin Calcium Injection USP and Tablets: “Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone, and increase the frequency of seizures in susceptible children” (Novartis New Zealand Ltd, 2014; Hospira NZ Ltd, 2015).

These Data Sheets also noted that the calcium folinate could enhance the toxicity of fluoropyrimidines such as 5-fluorouracil and that high doses of calcium folinate would reduce

the efficacy of intrathecally administered methotrexate (Novartis New Zealand Ltd, 2014; Hospira NZ Ltd, 2015). The APO-FOLIC Data Sheet noted that folate depletion is a side effect of folate antagonists such as 5-fluorouracil, methotrexate, trimethoprim, pyrimethamine and sulphonamides. It then went on to say that potentially severe deficiencies may be treated with calcium folinate therapy. However, all of these medicine classes would be expected to be taken under the supervision of a medical practitioner so it would be expected that people would not be at risk of taking both without being under medical supervision.

Incompatibilities with folic acid supplementation that have been noted in Data Sheets on the Medsafe website include droperidol, foscarnet injection, sodium bicarbonate and phosphonosulphate (Novartis New Zealand Ltd, 2014; Hospira NZ Ltd, 2015).

The Data Sheet for APO-FOLIC (Apotex NZ Ltd, 2007) noted that:

- Folic acid may interact with antacids which contain aluminium or magnesium, antibiotics and cholestyramine, sulphonamides including sulphasalazine and zinc supplements.
- The requirements for folic acid may be increased in patients receiving analgesics, anticonvulsant particularly hydantoin and carbamaepine, oestogens and oral contraceptives.
- Chronic alcoholism decreases the absorption of folic acid. Abstinence from alcohol will partially reverse this effect.

Possible risk arising from possible interactions with medicines can be mitigated for NHPs by including a label advisory statement to the effect:

> *Folate supplementation can mask a vitamin B12 deficiency or interfere with medicines that affect folate metabolism. Consult a health care practitioner prior to use*.

7. Contraindications and precautions.

Contraindications noted in the Data Sheets of medicines containing folic acid (Apotex NZ Ltd, 2007; Novartis New Zealand Ltd, 2014; Hospira NZ Ltd, 2015) reviewed are:

- Hypersensitivity to folic acid.
- Megaloblastic anaemia resulting from cyanocobalamin (Vitamin B12) deficiency should not be treated with folic acid as the neurological defects of vitamin B12 deficiency will not be alleviated, and may become irreversible.
- Caution is advised in patients who may have folate-dependant tumours.

Warnings and Precautions (that have not already been noted elsewhere) (Apotex NZ Ltd, 2007):

- Patients receiving concurrent administration of diphenylhydantoin and folic acid should be monitored for possible loss of seizure control.
- Folic acid does not correct folate deficiency due to dihydrofolate reductase inhibitors, such as methotrexate. Folinic acid should be used for this purpose.
- Folic acid should not be added to multivitamin preparations as it may lower the concentration of vitamin B12 in the blood.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

In double blind randomised placebo controlled clinical trials involving a multi-ingredient essential nutrient formulation also containing zinc, the following adverse events were reported (Rucklidge et al, 2014; Gordon et al 2015):

> Headache, dry mouth, sleep disruption, gastrointestinal disturbances, nausea, constipation, agitation, sedation, anxiety, rash (diagnosed by the consulting psychiatrist as being unrelated), abdominal pain, weight gain, blurred vision.

There was no reported to be no significant difference in adverse events between the trial groups and placebo groups. One absence seizure was reported in one of the trials, but further investigations were unable to determine whether there was a seizure, or whether the observer had misinterpreted the event. As the products are a multi-ingredient product, any causal link to any particular ingredient is problematic.

However, some reports indicate that doses of 5 mg per day can cause abdominal cramps, diarrhoea, and rash (Title et al, 2000). Folic acid 15 mg per day can sometimes cause altered sleep patterns, vivid dreaming, irritability, excitability, overactivity, confusion, impaired judgment, exacerbation of seizure frequency and psychotic behaviour, nausea, abdominal distension, flatulence, bitter taste in the mouth, allergic skin reactions, and zinc depletion (McEvoy, 1998).

The requested maximum daily dose of 1000 µg (1 mg) is well below the levels mentioned in these reports.

The following reported adverse reactions are taken from the data sheets of folic acid medicines from various companies:

Ebewe
Adverse reactions to calcium folinate are rare. Occasional hypersensitivity reactions have been reported; pyrexia, urticaria and anaphylactoid reactions have occurred after parenteral administration. Nausea and vomiting with very high doses of calcium folinate have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually in association with fluoropyrimidine administration.

DBL
Allergic sensitisation, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folic acid. Nausea and vomiting with very high doses of Calcium Leucovorin have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving Calcium Leucovorin, usually in association with fluoropyrimidine administration.

Apotex
Folic acid is generally well tolerated.
Although uncommon, nausea diarrhoea, flatulence and gastro-intestinal disturbances have been associated with folic acid therapy.
Hypersensitivity reactions such as bronchospasm, erythema, fever rash or itching have been reported rarely.

10. Potential for abuse or misuse.

Folic acid is not habit-forming or a drug of abuse.

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