

16 March 2022

An Open letter to the Medicines Classification Committee:

To the Members of the Medicines Classification Committee,

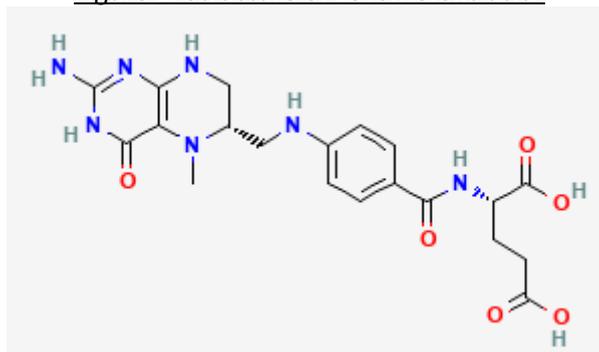
We, Natural Health Products New Zealand, on behalf of our members in the New Zealand Natural Health Products industry, submit this letter to the Medicines Classification Committee in response to the potential classification of levomefolate as a medicine in New Zealand, as per the agenda of the 68th meeting of the Medicines Classification Committee (MCC)¹.

Natural Health Products New Zealand is the peak industry body representing over 80% of the sector. Our members include manufacturers of ingredients and consumer brands of dietary supplements and functional foods.

Natural Health Products New Zealand seek to ensure the currently permitted use of levomefolate in foods, supplemented foods and dietary supplements in New Zealand continues. Classification as a medicine would restrict consumer choice and significantly hinder the industry's ability to export product globally, unless provisions are made to ensure its current permitted use remains unaffected. Folate (Vitamin B9) has been identified as essential to human health and nutrition as a coenzyme critical for DNA synthesis and cell reproduction². Levomefolate is the predominant naturally occurring form of folate in foods and the active metabolite our body converts folic acid into³. It is also the predominant form in folate found in breast milk⁴.

Levomefolate, Chemical formula C₂₀H₂₅N₇O₆, is listed in the literature and regulatory approvals worldwide as many different synonyms, including but not limited to levomefolate, levomefolic acid, L-methyltetrahydrofolic acid, L-methylfolate as well as the common salt form L-methyltetrahydrofolate calcium.

Figure 1: Structure of Levomefolic acid⁵



¹ Agenda for the 68th meeting of the Medicines Classification Committee. Accessed online at <https://www.medsafe.govt.nz/profs/class/Agendas/Agen68/agen68.htm>

² Nutrient Reference Values for Australia and New Zealand. Accessed online at <https://www.nrv.gov.au/nutrients/folate>

³ JEFCA Chemical and Technical Assessment of Calcium L-5-methyltetrahydrofolate, 2005. Accessed online at <https://www.fao.org/3/at980e/at980e.pdf>

⁴ Page et al 2019. Total folate and unmetabolized folic acid in the breast milk of a cross-section of Canadian women. Accessed online at <https://pubmed.ncbi.nlm.nih.gov/28298392/>

⁵ Pubmed structure. Accessed online at <https://pubchem.ncbi.nlm.nih.gov/compound/Levomefolic-acid#section=3D-Conformer>

Levomefolate (and its salts) has substantial global recognition as a safe form of folate and is widely permitted for use in foods and health supplements in many markets worldwide. Levomefolate has GRAS (Generally Recognized as Safe) status, allowing its use as a dietary ingredient in infant formula, foods and dietary supplements in the United States ⁶.

Table 1: Summary of Levomefolate Permitted Use Classification

Country	Regulating Body	Product Class	Permitted use
New Zealand	MPI/Medsafe	Dietary Supplement	Not restricted
New Zealand	MPI	Supplemented food	Permitted as a form of Folate as Methyltetrahydrofolate calcium up to a MDD of 500 mcg ⁷ (requires advisory statement for doses 200-500 mcg for consumption only by persons of or over the age of 14 years)
Australia and New Zealand	FSANZ/MPI	Food	Permitted as a form of folate as L-methyltetrahydrofolate, calcium ⁸
Australia	Therapeutic Goods Administration	Listed Medicine	Permitted as either levomefolate calcium or levomefolate glucosamine as an active ingredient in up to an equivalent MDD of 500 mcg levomefolic acid ⁹
Canada	Health Canada	Natural Health Product	Permitted as form of Vitamin folate up to MDD of 1000 mcg. Permitted as: L-5-Methyltetrahydrofolate L-5-Methyltetrahydrofolate, calcium salt L-5-Methyltetrahydrofolic acid, glucosamine salt ¹⁰

⁶ GRAS notice for the use of calcium l-methylfolate in infant formula. GRAS Notice (GRN) No. 915. Accessed online at <https://www.fda.gov/media/140366/download>

⁷ Supplemented food standard user guide - Appendix 2: Vitamins and Minerals: Permitted Forms and Maximum Quantities. Accessed online at <https://www.mpi.govt.nz/dmsdocument/13092-Supplemented-food-standard-user-guide>

⁸ Australia New Zealand Food Standards Code – Schedule 17 accessed online at <https://www.legislation.gov.au/Details/F2021C00328>

⁹ Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2022 Schedule 1, Entries 3012 and 3013. Accessed online at <https://www.legislation.gov.au/Series/F2022L00173>

¹⁰ Natural Health Products Ingredients Database Accessed online at <http://webprod.hc-sc.gc.ca/nhp-id-bdipsn/search-rechercheReq.do>

Country	Regulating Body	Product Class	Permitted use
Singapore	Health Sciences Authority	Quasi-Medicinal Product for supplemental purposes	0.9 mg Folic Acid (derived from the following source material(s): L-5-Methyltetrahydrofolate, L-5-Methyltetrahydrofolate calcium salt, L-5-Methyltetrahydrofolate acid glucosamine salt) ¹¹
USA	FDA	Dietary Ingredient in Foods/Dietary Supplement	Generally recognised as safe – Upper tolerable limit 1 mg folate/day ¹²
EU	EFSA	Food, Food supplements, Foods for special medical purposes, Total diet replacement for weight control.	Calcium-L-methylfolate permitted up to tolerable Upper Limit of 1 mg folate/day ^{14,15}

In 2004, a review conducted by the European Food Safety authority (EFSA) Scientific panel also assessed the use of L-methyltetrahydrofolate calcium as a source of folate in foods and concluded it does not pose a safety concern up to a maximum combined intake (from folic acid and L-5-MTHF-Ca) in adults of 1 mg per day¹³. It is now authorised for use in food supplements and foods as per EC Regulation 1170/2009¹⁴ as well as in foods for special medical purposes and total diet replacement for weight control as per Regulation (EU) No 609/2013¹⁵. A 2020 safety review by the EFSA NDA Panel for the European commission, also concluded that its use is safe for infants and young children¹⁶.

A 2008 FSANZ report concluded that levomefolate calcium does not pose any public health or safety concerns and should be approved for use in fortified foods as a permitted source of folate¹⁷. As a result of this report, Levomefolate in its calcium salt form (L-methyltetrahydrofolate calcium) is now currently permitted in foods as a source of folate in Australia and New Zealand as per “Schedule 17-2 Permitted forms of Vitamins” of the Food Standards Code¹⁸. Schedule 4 of the Food Standards code

¹¹ Singapore HAS Complementary Health Products (CHP) Classification Tool. Accessed online at <https://www.hsa.gov.sg/chp-classification-tool>

¹² National Institute of Health Folate Fact Sheet for Health Professionals. Accessed online at <https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/>

¹³ Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium L-Methylfolate. The EFSA Journal (2004) 135, 1-20. Accessed online at <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2004.135>

¹⁴ COMMISSION REGULATION (EC) No 1170/2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. Accessed online at <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32009R1170&from=EN>

¹⁵ (EU) No 609/2013 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control. Accessed online at <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32013R0609&from=en>

¹⁶ Calcium L-methylfolate as a source of folate added for nutritional purposes to infant and follow-on formula, baby food and processed cereal-based food. Accessed online at <https://doi.org/10.2903/j.efsa.2020.5947>

¹⁷ <https://www.foodstandards.gov.au/code/applications/documents/A566%20L-Methylfolate%20FAR%20FINAL.pdf>

¹⁸ Australia New Zealand Food Standards Code – Schedule 17. Accessed online at <https://www.legislation.gov.au/Details/F2021C00328>

also permits a number of general level health claims for Folate recognising its importance in general health and wellbeing including “Contributes to maternal tissue growth during pregnancy”, “Necessary for normal cell division” “Necessary for normal blood formation”¹⁹.

The outdated Dietary Supplement Regulations (1985) in New Zealand are already posing significant barriers to trade with our higher-regulated export partners. There is currently no exemption in New Zealand for companies to manufacture natural health products as “export only” should products made for export not meet New Zealand compositional requirements, thus any potential restrictions on the use of levomefolate in foods or dietary supplements in New Zealand, will further impede our industry’s ability to export to the fast-growing natural health product global market.

We would also like to inform the MCC and remind Medsafe that we represent stakeholders who have not been consulted on the proposed medicines classification of levomefolate and should have been. We have been informed that the composition of the MCC is mandated by the Medicines Act, however as our industry will be directly affected by any classification of levomefolate as a medicine, it is in the best interests of New Zealand consumers and industry that we are permitted to have a voice in such matters and we do not understand why this has not happened. We request that MCC and Medsafe do consult with us on such matters in the future and request engagement to establish a forum where this can and does occur.

We request that the MCC consider these implications and ensures the currently permitted use of levomefolate in foods, supplemented foods and dietary supplements in New Zealand in dosages in accordance with the majority of international regulators (up to 1mg per day) is maintained. This is further supported by the 56th MCC Meeting agenda item for Folic Acid where the recommendation was also up to 1mg per day.

Yours sincerely

Members of Natural Health Products New Zealand



Samantha Gray
Government Affairs Director

¹⁹ Australia New Zealand Food Standards Code – Schedule 4 – Nutrition, health and related claim. Accessed online at <https://www.legislation.gov.au/Details/F2017C00711>