Submission for medicine reclassification for consideration by the Medicines Classification Committee

This form should be completed in conjunction with the directions in the guidance document 'How to change the legal classification of a medicine in New Zealand'.

Please also complete an introduction summarising the intention of the submission and provide any relevant background.

Once completed, this application should be sent to the MCC Secretariat (committees@health.govt.nz) by the deadline on the dates and deadlines page on the Medsafe website.

By submitting this form, you are confirming that all information is true and accurate, and understanding that this information and any appendices and/ or supporting information that is not considered commercially confidential under the Official Information Act 1982 will be published on the Medsafe website.

Introduction

Please provide background context for the submission

Lithium regardless of dose, has historically been viewed as a medicine in NZ. It is used to treat Bipolar Disorder although other conditions can also respond to lithium treatment. The lithium used therapeutically is usually lithium carbonate and the doses typically start at 250mg. This historical context has resulted in a broader public consciousness still clearly associating lithium with drug status and toxicity, leading to inferences that lithium is not nutritional for humans. This persistent perspective may in part be because academic and regulatory bodies worldwide have ossified around the burst of nutritional discoveries in the 20th century (with the accompanying food fortification programs, etc.), and have been slow to formally recognize the beneficial nature and probable essentiality of trace nutrients in recent years. Lithium has been especially disadvantaged in gaining recognition as an essential nutrient, because it did not enter the era of nutritional research on neutral ground. Various lithium salts were used medically from the mid 19th century, and after 1949 it became a prescription status medicine.

In contrast, lithium orotate is used overseas as a dietary supplement and New Zealanders import it via iherb and other platforms for personal use. The dose is much lower and therefore does not carry the risks associated with doses used to treat serious mental health disorders. Like other nutrients that have a DS and a medicine classification (e.g. vitamin D), it is well overdue that the same happen for lithium.

Please note that some of the information contained in this application came from previous applications submitted to the MCC by the natural products industry (available online) as well as documents submitted to Medsafe as part of discussions on whether a multinutrient product is classified as a medicine or a dietary supplement due to the presence of trace amounts of lithium contained within it (Daily Essential Nutrients - DEN). However, I have not consulted with the company that makes DEN on this application – I come from the perspective of supporting New Zealanders to manage their health with safe options. I am not funded by the industry and have never received any funding from companies that make natural health products.

Part A- Regulatory Context and Proposed Classification

1. International non-proprietary (INN) name of the medicine

Lithium

2. Proprietary names (if applicable)

N/A

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

Contact details can be removed from the form prior to publication of the Medsafe website if requested.

Prof Julia Rucklidge
[redacted]
[redacted]

[redacted]

4. Dose form(s) and strength(s) for which a change is sort (if applicable)

N/A

5. Pack size, storage conditions and other qualifications (if applicable)

N/A

6. Indications for which change is sought (if applicable)

N/A

7. Present classification of the medicine

As far as I know, at the present time, lithium is:

• Unscheduled when in medicines for dermal use containing 0.01% or less. [0.01% is equivalent to 100 ppm].

• Unscheduled when present as an excipient in medicines for dermal use containing 0.25% or less.

• Pharmacy-only medicine when in medicines for dermal use containing 1% or less but more than 0.01%.

• Pharmacy-only medicine except when present as an excipient in medicines for dermal use containing 0.25% or less.

• Prescription medicine except in the above circumstances.

It is noted that the Schedule, as currently expressed, allows lithium to be present in higher amounts in medicines for dermal use if it is declared as an excipient, than is allowed when it is declared to be an active ingredient. It is requested that the MCC review the way the entry for Lithium is phrased in the Medicines schedule.

8. Classification sought

It is proposed that the classification of lithium is changed to:

• Unscheduled when present in products for dermal use containing 0.01% or less.

• Unscheduled when present in products for internal use containing no more than 3 mg of lithium as the recommended daily dose.

• Pharmacy-only medicine when in products for dermal use containing more than 0.01% but less than 1.0%.

• Prescription medicine except in the above circumstances.

9. Classification status in other countries (especially Australia, UK, USA and Canada), and any justification for harmonisation

Australia

Lithium is:

• Unscheduled when in preparations containing 0.01 per cent or less of lithium.

• Schedule 2 (Pharmacy medicine) when in preparations for dermal use containing 1 per cent or less of lithium except:

(a) when present as an excipient at 0.25 per cent or less of lithium; or

(b) in preparations containing 0.01 per cent or less of lithium.

• Schedule 4 (Prescription medicine) except:

(a) when included in Schedule 2

(b) when present as an excipient in preparations for dermal use containing 0.25 per cent or less of lithium; or

(c) in preparations containing 0.01 per cent or less of lithium.

Canada

Lithium is a Schedule 1 substance (ie, can only be obtained on prescription) in medicinal products. It is considered to be a non-NHP substance, but is allowed to be used in homoeopathic preparations.

UK

Lithium compounds are scheduled as either Pharmacy medicines or Prescription medicines.

USA

Lithium orotate is a DS.

10. Extent of usage in New Zealand and elsewhere (e.g. sales volume) and dates of the original consent to distribute

As far as I am aware, there is no information on the extent of dietary supplement / natural health type of products in New Zealand that contain lithium. It is legally not allowed in DS doses in supplements sold in NZ given its classification as a medicine. There are hundreds of dietary supplement-type products containing lithium available in the USA, with many of these products containing lithium at doses of 5 mg to 20 mg. None of these are legally allowed to be sold as a DS in NZ.

11. Local data or special considerations relating to New Zealand (if applicable)

Lithium is only available in NZ as a prescription medicine. It is available in capsules of 250mg of lithium carbonate. As a DS the form is typically lithium orotate.
In my own research and a study overseas, we tested serum lithium levels, along with blood levels of other nutrients when given as lithium orotate at 1mg per day as part of a multi-ingredient product (Daily Essential Nutrients). Lithium was undetected in these tests, demonstrating that 1mg of lithium is not reaching therapeutic levels as per lithium carbonate (Robinette et al., 2023; Rucklidge et al., 2018).

Nutritional lithium intake from food

Compelling evidence that a concentration of 10 ppm is in the realm of nutritional rather than therapeutic use comes from the fact that several foods widely consumed in New Zealand may exceed this concentration. Published analyses of almonds from the USA, Spain, and Turkey averaged 10.46 ppm lithium with a standard deviation of 6.694 ppm, and peanuts from the same countries have been analysed at 8.953±6.469 ppm lithium (Gonzales et al., 2013). As evidenced by the high standard deviation, some samples of these crops could very possibly contain more than double the 10 ppm drug concentration cutoff. The fact that these results were found in nuts grown in different parts of the world may mean that these lithium levels are typical of the food no matter where it is grown. An alternative explanation of the data could be that the pooled average and standard deviation are both high due to select crops from certain regions that are skewing the data. Whatever the reason for the high lithium concentrations in these food products, the fact that some apparently exceed Medsafe's current drug concentration cutoff would suggest that 10 ppm is an inappropriately low concentration to consider a drug. Furthermore, this highlights the fact that total daily intake, which is the metric used for other dietary components, is a more appropriate measure than concentration. This obviously calls into question the ability of any regulatory agency to enforce a rule for such a low lithium concentration proportionately.

A natural dosing limitation exists in the nature of lithium orotate itself: it is a bulky, low concentration source of lithium (~3.8% lithium) in comparison to lithium carbonate (~18.8% lithium). It is difficult to fit enough lithium orotate in a single capsule to deliver much more than 5 mg of elemental lithium at a time. The question might be asked, "If no other form (i.e. salt) of lithium apart from lithium carbonate has been approved for sale as a drug in New Zealand and consumers are not likely to use them at therapeutic doses, why are they then regulated as drugs down to such a low quantity as to exclude them from the New Zealand market?" Although the intent may be to provide safe and regulated drugs for the New Zealand population, the net effect is simply to completely restrict access to these products within New Zealand. The extensive and overwhelmingly safe use of lithium orotate as a dietary supplement in the U.S. market provides strong evidence that choosing to exercise extremely restrictive enforcement discretion is simply not necessary from the point of view of safety and may actually be harmful given that lithium appears to have clear nutritional benefits.

12. Labelling or draft labelling for the proposed new presentation(s) (if applicable)

N/A

13. Proposed warning statements (if applicable)

N/A

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

Manufacturers of current dietary supplement-type products may introduce products containing lithium at the allowed maximum daily dose. Currently approved medicines on the New Zealand market that contain lithium are:

1. Lithicarb FC 250 mg and 400 mg film coated tablets Lithium carbonate 250 mg capsules
2. Priadel 200 mg and 400 mg modified release tablets Sofradex ear/eye drops (containing lithium chloride as an excipient)

These medicines contain lithium at significantly higher quantities than the requested change of up to 3 mg per recommended daily dose. They will not be affected by the requested change.

Part B- Clinical Context and Implications

15. Indications and dose

- *What is the medicine indicated for, and for which indication(s) is the reclassification application for?*
- *What is the evidence that the proposed indication is an OTC indication ie, that the diagnosis and treatment can be understood by the consumer; that the risks of inappropriate treatment can be minimised?*
- *What is the treatment population for the indication (age, gender etc.)?*
- *What is the dose and dose frequency of the medicine for this indication?*

Lithium is found in trace amounts in the soil and is taken up by plants and vegetables. It has also been found dissolved in water in varying levels of 1ug/L to 500 ug/L, in proportion to the environmental soil levels. Consequently, the main sources of dietary intake of lithium in humans are grains and vegetables. However, the actual intake of lithium as part of the diet is strongly dependent on the environmental levels of lithium in the soil and drinking water (Schrauzer, 2002). More recently, lithium has become available as a dietary supplement available on various internet websites (e.g. Amazon.com, iherb.com).

16. Presentation

- *What is the proposed dose form and strength of the medicine to be reclassified? Is this the same for all indications?*
- *What disposal considerations need to be made for the medicine?*
- *How practical and easy to use is the proposed presentation?*

N/A

17. Consumer benefits

- *What is the history of this medicine's use for the proposed indication(s) ie, number of users; number of countries used in?*
- *To what extent is this medicine used for the proposed indication(s) ie, duration of use; frequency of use?*

- *What is the evidence that improved access is beneficial for the individual?*
- *What is the evidence of improved consumer involvement in their health?*
- *What are the benefits from a consumer viewpoint?*

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 1985 regime (which is likely going to be the regulatory framework for at least the next few years if not longer if history is a guide to go by), 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 clear benefit of allowing the requested change is that it will finally allow an essential mineral to be present in dietary supplements.

Lithium is involved with many physiological functions. It works with other elements, drugs, enzymes, hormones, vitamins, and growth and transforming factors. Theoretically, many of the biological actions of lithium are caused by the powerful polarizing effect caused by its small atomic radius, allowing it to displace sodium, potassium, magnesium, and calcium from membrane or enzyme binding sites (Schrauzer, 2002). Lithium is normally present in all organs and tissues, with highest concentrations in the brain and kidneys. Lithium has been shown to have considerable neuro-protective effects, even in trace or low doses. Lithium, in both standard and trace doses, appears to have biological protective benefits for dementia, suicide, and other behavioural outcomes (Mauer et al., 2014). In some geographical areas, drinking water may contribute significantly to lithium intake (Schrauzer, 2002; Zarse et al., 2011). Epidemiological evidence suggests that areas with lower lithium content in tap water have higher rates of mental hospital admissions, suicides, homicides, and other crimes, suggesting that lithium intake might affect behaviour (Giotakos, 2018). Lithium appears to be essential for foetal development, particularly during the first trimester of gestation. It appears to have a role in foetal blood cell development (Schrauzer, 2002).

Trace and Low Dosing Lithium Research

Lithium has been used as a treatment for manic depression since the 1940s (Hamstra et al., 2023). It is usually administered in high doses (900-4000 mg/day), sometimes resulting in serious adverse effects. However, there is a growing body of literature showing the protective effects of much lower (and safer) amounts of lithium.

The Royal Australian and New Zealand College of Psychiatrists conducted a review in 2014 on the administration of trace or low dose lithium for the prevention of dementia

and other behavioural disorders (Mauer et al., 2014). Nine out of 11 epidemiological studies on lithium – usually from drinking water sources – found an association between trace-dose lithium and low suicide/homicide/mortality and crime rates. Five out of seven epidemiological studies found an association between standard-dose lithium and low dementia rates. Although standard lithium concentrations of 0.6 – 0.8 mMol/litre (4.0 – 5.0 mg/litre) have the most benefit for enhancing neuronal viability, even 'low' levels of 0.2–0.4 mMol/litre (1.39 – 2.77 mg/litre) have some benefit (Hashimoto et al., 2002). Trace levels of lithium would be undetectable in standard blood tests, which generally do not measure lithium levels below 0.2 mMol/litre. But, in some of the available animal research, even concentrations below 0.2 mMol (1.39 mg/litre) lead to enhanced neuronal viability (Hashimoto et al., 2002). The implications for protecting the elderly from cognitive decline through simple supplementation should be celebrated given the potential cost savings, even if not all citizens are taking supplements.

Lithium has been shown to reduce overall mortality in humans in a study involving a cohort of 1,206,174 people (18 municipalities in Japan), with varying levels of lithium in their tap water (Zarse et al., 2011). Mortality rates were compared, showing that higher lithium levels in tap water corresponded with lower overall mortality rates. The life-span of a Caenorhabditis elegans (roundworm) was also measured when exposed to comparable concentrations of lithium. This roundworm is commonly used for anti-aging studies. Overall, it was found that lithium chloride extends the life-span of C. elegans (Zarse et al., 2011).

Mental health is a rising concern in New Zealand with estimates of 20% of the population struggling with a mental health condition in any one given year. Lithium supplementation in low, non-toxic doses may promote mental health. Indeed, lithium in trace amounts, as occurs in drinking water, has been inversely related to suicidal mortality, aggression and homicidal violence (Giotakos, 2018).

Considering lithium through the lens of other beneficial dietary nutrients highlights the unusual and disproportionate nature of treating as a drug low-dose quantities of lithium which are within the range of normal dietary intake. Aside from man-made categorizations, the natural difference between lithium and most other dietary trace minerals is negligent. Like lithium, other vitamins and minerals are naturally occurring, naturally present in the diet, known to be beneficial to human health, and at increasingly higher doses they exert both medically significant therapeutic effects and eventual toxicity.

Importantly, just as for the other nutritional micronutrients, there is substantial evidence that lithium intake within the range of normal dietary intake remediates apparent deficiency in humans.

18. Contraindications and precautions

- *What are the contraindications for the medicine and how easy are they to identify and prevent?*
- *What are the precautions for this medicine and how easy are these to understand?*
- *Does the medicine have a low therapeutic index?*
- *What class effects need to be considered and what are the risks?*
- *What are the risks of the medicine being used in an OTC environment?*
- *What other drug interactions need to be considered?*
- *What food and/ or drink interactions need to be considered?*
- *Are there any other restrictions when taking the medicine ie, driving restrictions or operating machinery?*
- *Are there any special populations where exposure to the medicine needs to be restricted?*

Indomethacin and piroxicam have been reported to increase steady-state plasma lithium concentrations (Martindale, 1999; McEvoy, 1998). Other NSAIDs including COX-2 inhibitors, may have a similar effect, but a definite link has not been established.

Diuretics, ACE inhibitors and ARBs may increase serum lithium concentrations. Generally, the interactions with NSAIDs, ACE inhibitors and ARBs are unpredictable and do not occur in all patients and concurrent use is not contraindicated (BPAC, 2007). At the proposed maximum level of 3 mg/day, it is considered that no interaction effect is likely to occur with medicines.

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, and to patients receiving diuretics, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity (Drugs.com, 2016). However, as stated above, the toxicity level is close to the therapeutic level (starting dose at 600 mg lithium carbonate). Lithium increases brain serotonin, and caution should be taken when it is used with other medicines that also affect serotonin levels, such as other anti-depressant drugs and monoamine oxidase inhibitors. However, at the level of the proposed change, this risk is unlikely to be present for DS doses.

These risks could be included as part of the labelling as per other supplements with nutritional levels of minerals contained within them.

19. Undesirable effects

- *What are the known undesirable effects and the frequencies of these? Do these vary for special populations?*
- *What are the risks and consequences of known undesirable effects?*
- *Are there any significant safety concerns for the medicine under review?*
- *Have there ever been any withdrawals of the medicine or other regulatory actions taken for safety reasons (during a time period or in a specific jurisdiction)?*
- *Are there any withdrawal effects following cessation of use of the medicine?*

Lithium was banned by the FDA in 1949 after deaths of heart patients who had been prescribed lithium chloride as a substitute for salt. However, these were mega-doses of up to 14g/day (14,000 times higher than the current suggested RDA of 1mg). Lithium was re-approved in 1972 for use in relatively high doses (150mg/day) in carbonate form as a drug, primarily in the treatment of bipolar disorder. Toxicity at these high doses is managed by patients taking regular blood tests to monitor lithium levels, which should be between 0.4 to 1.0 mmol/L.

There is no established Tolerable Upper Intake Level for lithium. Low dose nutritional lithium in orotate form (1-20mg daily) as part of a multinutrient has not been associated with toxicity or adverse events. The only reported toxicity case in the literature was of a deliberate overdose of 18 120mg lithium orotate pills (Pauzé & Brooks, 2007), giving a total dosing of more than 2g. The patient experienced one occurrence of vomiting and displayed a mild tremor which resolved within hours, with no long-term deleterious effects.

Lithium deficiency has been linked to altered behaviour and aggressiveness in humans (Schrauzer, 2002). In another study, Schrauzer et al also showed an inverse relationship between water Li levels and psychosis, neurosis, and personality disorders. He further goes on to suggest that establishing an adequate intake level may be beneficial to individual health and overall society.

Acute Li poisoning may present with gastrointestinal, cardiac, or neurologic symptoms. This may encompass nausea, vomiting, diarrhea, ECG changes (prolonged QTc, bradycardia), ataxia, confusion, tremors, fasciculations, or myoclonic jerks. Neurologic manifestations are a later presentation in the sequelae of acute Li poisoning. Chronic Li poisoning on the other hand presents with fewer GI symptoms and is more likely to present with initial neurologic symptoms (Jeanmarie Perrone, 2016).

These potential risks, however, exist when using lithium in therapeutic levels. For example, lithium as carbonate dosing in children 6-12 years is anywhere from 15-60 mg/kg/day for bipolar disorder and 15-30 mg/kg/day for conduct disorder. These doses are far higher than the dose proposed here for a DS.

20. Overdose

- *Is there a potential for overdose of the medicine?*
- *What are the consequences of overdose of the medicine?*
- *Are there any reports of overdose of the medicine?*

N/A

21. Medication errors and abuse/ misuse potential

- *Would reclassification affect the risk of unnecessary use?*
- *Should the medicine be provided with necessary tools to allow correct dosing eg, liquids supplied with a measuring device?*
- *What are the reported medication errors post-market?*
- *What are the reported cases of abuse/misuse/accidental overdose?*
- *How would reclassification affect import considerations?*
- *What is the addiction potential of the medicine?*

N/A

22. Communal harm and/or benefit

- *What are the possibilities of community harm resulting from wider use of the medicine in question (e.g., the development of antibiotic resistance in bacteria or increased immunisation rates)?*
- *What are the possibilities of community benefit resulting from wider use of the medicine in question (e.g., greater herd immunity as a result of improved access to a communicable disease vaccine)?*

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand's does not include recommended intakes for lithium. The International Association of Dietary and Food Supplement Associations (IADSA) does not include recommendations regarding lithium. The European Food Safety Authority considered an application for a lithium-enriched yeast added for nutritional purposes as a source of lithium in food

supplements and concluded that they were unable to conduct a proper assessment for lack of an appropriate dossier supporting its use (EFSA 2009).

A provisional recommended daily allowance of 1 mg/day for a 70 kg adult has been suggested (Schrauzer, 2002). Primary dietary sources include drinking water, grains and vegetables, with smaller amounts being obtained from animal-derived foods (Zarse et al., 2011). The average daily intake of an American 70 kg adult ranges from 650–3100 µg (0.65 – 3 mg). The US Environmental Protection Agency is reported to have recommended a Tolerable Daily Intake (TDI) of 0.02 mg/kg/day. In a study of lithium levels in New Zealand soils, and the potential for risk of lithium toxicity from eating vegetables grown on New Zealand soils, Yalamanchali (2012) concluded that the EPA's TDI would not be exceeded even if the plant that sequestered the most lithium from lithium-uncontaminated soil was consumed (one would have to eat 5 kg of beet root daily to approach the TDI).

The main concern over the safety of lithium is that the toxic level is close to the therapeutic level. Lithium is used in the therapeutic treatment of manic episodes, where lithium carbonate is prescribed at 600 mg t.i.d. in order to obtain a serum level of around 1.0 to 1.5 mEq/litre. Dosage is usually individualised according to serum levels and clinical response. Long term, maintenance doses are individualised to achieve a desired serum level of 0.6 to 1.2 mEq/litre for optimal patient response (about 300 mg t.i.d. or b.i.d). Treatment for poisoning is usually through cessation of treatment and then resumption of the treatment at a lower dose after 24 to 48 hours. The proposed change to allow for the presence of lithium at up to 3 mg daily in natural health products, particularly as a trace element, is a couple of orders of magnitude below the toxic level. No risk is considered to be posed at this level, and precautions are considered to be unnecessary.

23. Integrated benefit-risk statement

- *A summary of the reclassification benefits*
- *A summary of the reclassification risk of harm*
- *A summary of the need for the medicine at the classification proposed*
- *Precedent – how are other medicines in the same class classified?*

Vitamin D and zinc are both a DS and a medicine, depending on dose.

24. Risk mitigating strategies

- *Are there any risk mitigation strategies required? If so, what risk mitigation strategies are required e.g., healthcare professional education; integration of care; consumer information to be provided etc?*
- *What is the evidence that these proposed risk mitigation strategies would be effective?*
- *What post-market surveillance activities would be carried out?*
- *Is the proposed reclassification supported by professional bodies?*

This reclassification has been supported by the industry for decades and indeed, they submitted for this exact change to occur in 2016. The industry would welcome the opportunity to be able to use small amounts of lithium in their products for both local and overseas exports. New Zealanders would benefit from supplements containing small amounts of lithium.

Conclusion

A brief summary of the purpose of the submission and any concluding remarks

I ask the MCC to consider exercising more appropriate enforcement discretion by applying the methodology intended for nutritional components of diet to lithium. There is a large body of literature which clearly demonstrates that lithium intake exceeding 3 mg/day is within the normal dietary range. Given that some individuals have very low lithium intake due to the increasingly nutritionally depleted diets of the 21st century (due to the increasing consumption of ultra-processed foods, very low in essential nutrients), doses of supplemental lithium up to at least 3 mg/day should be viewed as nutritional rather than therapeutic.

Since it is neither justifiable from the scientific literature for lithium nor proportionate with the enforcement of other nutritional components of diet to transition to prescription status within the range of normal dietary intake, I ask that the use of an appropriate UL as a reference limit for dietary supplement categorization rather than the current 10 ppm concentration or any value within the range of normal dietary intake, including the provisional RDI of 1 mg/day.

3 mg of Li is less than 0.5% of a therapeutic Li regimen for adults using lithium as treatment for mood disorders. There is no data to suggest that this dose is toxic. Lithium in nutritional form (orotate) and dosage level (1-20mg/day) has an excellent safety record and provides a range of health benefits and should not be confused with lithium in medicinal form (carbonate) and dosage level (150mg/day and above), where toxicity must be carefully monitored; 3mg lithium/day is at a similar level to what might be consumed via food and drinking water.

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Please provide references for your submission

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