Submission for Lithium

Part A

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

Lithium.

2. Proprietary name(s).

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

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.

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, Canada).

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.

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

There is no information on the extent of dietary supplement / natural health type of products in New Zealand that contain lithium.

There are over 108 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.

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

Not applicable. Presumably the labels will be the same as those in Appendix 1.

12. Proposed warning statements if applicable.

Not applicable.

13. Other products containing the same active ingredient(s) and 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:

Lithicarb FC 250 mg and 400 mg film coated tablets
Lithium carbonate 250 mg capsules
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 Reasons for requesting classification change including benefit-risk analysis. This section should be supported by the following:

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 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. A number of products that might be prevented from being able to be considered natural health products because the content of lithium is higher than 0.01% (or 100 ppm) can be made available.

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 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. 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).

<u>Trace and Low Dosing Lithium Research</u>

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. All four small randomized clinical trials of lithium for Alzheimer's dementia have found at least some clinical or biological benefits versus placebo.

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, compared to placebo (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).

Lithium has been used as a treatment for manic depression since the 1940s (Fierro, 2015). It is usually administered in high doses (900-4000 mg/day), resulting in serious adverse effects. Results from a study to determine if low-dose naturally occurring lithium (vegetable-source) would have any benefit showed that just 150 µg naturally sourced lithium per day was just as effective as 300 – 900 mg lithium carbonate, without the side-effects. Thirteen manically depressive patients were given 50 µg of naturally occurring lithium with each of their meals for six weeks. Clinical improvement in all patients was observed after just 10 days of treatment. Considerable clinical improvement was observed in all patients after six weeks. The patients were taken off lithium and regressed to their former state of depression within 3 days. The patients were placed back on natural low-dose lithium and improved again after two days supplementation (Fierro, 2015).

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 round-worm 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. In 2013, a record number of people accessed specialised mental health and addiction services in New Zealand (3.5% of the population) (Ministry of Health, 2014). Lithium supplementation in low, non-toxic doses may promote mental health and reduce suicide risk, and may also reduce overall mortality in humans. Precedence would suggest that dosages below 5 mg per day would be very conservative, given that children are commonly prescribed upwards of 15 mg/kg of body weight.

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

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 be a 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.

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.

Not applicable.

6. Interactions with other medicines.

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.

7. Contraindications and precautions.

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 in Part B2 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.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

Signs of lithium toxicity include diarrhoea, vomiting, drowsiness, muscular weakness and lack of coordination. At higher levels (serum levels over 2.0 mEq/litre), giddiness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen.

10. Potential for abuse or misuse.

Lithium is not habit-forming or a drug of abuse. No abuse or misuse is foreseen.

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