Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for lithium, the scientific conclusions are as follows:

In view of available data on '*Brugada syndrome*' from spontaneous reports, including in three cases a close temporal relationship, positive de-challenge and/or re-challenge, and in view of a plausible mechanism of action, the PRAC Lead Member State considers a causal relationship between lithium and Brugada syndrome is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing lithium should be amended accordingly.

In view of available data on *'hyperparathyroidism', 'hypercalcaemia', 'parathyroid adenoma'* and '*parathyroid hyperplasia*' from the literature and spontaneous reports, including in some cases a positive de-challenge and/or re-challenge, and in view of a plausible mechanism of action, the PRAC Lead Member State considers a causal relationship between lithium and *'hyperparathyroidism', 'hypercalcaemia', 'parathyroid adenoma'* and '*parathyroid hyperplasia*' is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing lithium should be amended accordingly.

In view of available data on '*drug-drug interaction with topiramate*' from literature, including in three cases a close temporal relationship and positive de-challenge, the PRAC Lead Member State considers a drug-drug interaction between lithium and topiramate is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing lithium should be amended accordingly.

In view of available data on '*lithium toxicity following bariatric surgery*' from the literature, including in 12 cases a close temporal relationship, and in view of a plausible mechanism, the PRAC Lead Member State considers a causal relationship between lithium and toxicity following bariatric surgery is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing lithium should be amended accordingly.

In view of the available data on 'drug reaction with eosinophilia and systemic symptoms (DRESS)' from spontaneous reports and literature, including a close temporal relationship in six cases, of which two cases were with positive de-challenge after corrective treatment and positive re-challenge, the PRAC Lead Member State considers that a causal relationship between lithium and 'drug reaction with eosinophilia and systemic symptoms' is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing lithium should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for lithium the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing lithium is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

"…

Brugada Syndrome

Lithium may unmask or aggravate Brugada syndrome, a hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Lithium is not recommended in patients with known Brugada syndrome or a family history of Brugada syndrome. Caution is advised in patients with a family history of cardiac arrest or sudden death.

…"

- Section 4.8

The following adverse reaction should be added under the SOC Cardiac disorders with a frequency ***not known***:

Brugada syndrome (Unmasking/aggravation)

Package leaflet

Section 2. What you need to know before you take X

Warnings and precautions

Talk to your doctor before taking X

"…

If you have a condition called Brugada syndrome (a hereditary syndrome that affects the heart), or if anyone in your family has had Brugada syndrome, heart arrest or sudden death.

…"

Section 4. Possible side effects

"…

Frequency ***not known:***

Unmasking and/or aggravation of Brugada Syndrome (a hereditary syndrome that affects the heart)

…"

If existing wording is stricter it should be kept.

Summary of Product Characteristics

- Section 4.8

The following adverse reactions should be added under the SOC '*Endocrine disorders'*:

"…

Endocrine disorders: … ***hypercalcaemia*** <*frequency* ***very frequent***>***, hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia*** <*frequency* ***not known***>

…"

Package Leaflet

Section 4. Possible side effects

"…

Frequency very frequent

- ***too much calcium in your blood.***

Frequency not known

- ***Hyperparathyroidism (when the parathyroid glands produce too much parathyroid hormone, which raises calcium levels in the blood).***
- ***Increased size of the parathyroid glands.***
- ***Parathyroid adenoma (a non-cancerous tumour).***

…"

Summary of Product Characteristics

- Section 4.5

An interaction should be amended as follows:

"…

Topiramate

In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. There have been reports on lithium toxicity when concurrently administered with topiramate. Lithium levels should be closely monitored when co-administered with topiramate.

…"

Package Leaflet

Section 2. What you need to know before you take X

Other medicines and X

Tell your doctor or pharmacist if you are taking:

"…

Topiramate (used to treat epilepsy or migraine)

…"

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

"…

In patients who have undergone bariatric surgery, a lower maintenance dose of lithium may be required. Lithium levels should be closely monitored due to the risk of lithium toxicity until weight has stabilized.

…"

Package Leaflet

Section 2. What you need to know before you take X

Talk your doctor or pharmacist if you:

"…

Are planning, or have already had weight loss surgery, as a lower dose of lithium may be required. Your doctor will monitor the level of lithium in your blood and adjust your dose accordingly

…"

Summary of Product Characteristics

- Section 4.8

The following adverse reactions should be added under the SOC '*Skin and subcutaneous tissue disorders'* with a frequency ***not known***:

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package Leaflet

Section 4 – Possible side effects

Frequency ***not known***:

Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities

(eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome). Stop using <X> if you develop these symptoms and contact your doctor or seek medical attention immediately.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	9 June 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 August 2024