**Lithium carbonate**

Quilonium-R®

450mg Prolonged-release Tablet

**PRODUCT DESCRIPTION**

Each white to off-white, oblong, prolonged-release tablet contains 450mg (12.2mmol) of Lithium carbonate in a prolonged-release form.

Excipients: Povidone, Maize starch, Lactose monohydrate, Gelatin, Carboxymethylcellulose, Talc, Calcium arachinate, Magnesium stearate, Titanium dioxide, Macrogol 6000, Basic butylated methacrylate copolymer, Purified water, ethanol 96%, isopropyl alcohol.

**PHARMACOLOGIC PROPERTIES**

Pharmacodynamics

Mechanism of Action

Lithium is known to cause profound effects on a number of neurochemical systems including:

- ion channels
- neurotransmitters, including serotonin, dopamine and norepinephrine (NE)
- secondary-messenger systems such as phosphoinositides and cyclic AMP (cAMP).

Neurotransmitters

- Beta-Adrenergic: lithium increases the proportion of low-affinity beta receptors thereby reducing beta receptor function.
- Alpha-2-Adrenergic: lithium induces subsensitivity of alpha-2 receptors thereby increasing the release of norepinephrine.
- Serotonergic: lithium down-regulates some serotonergic receptor subtypes and increases serotonin turnover. This reduces negative feedback, thereby increasing the release of serotonin.
- Dopaminergic: lithium blocks the up-regulation of receptors when given concurrently with neuroleptics and increases dopamine concentrations and turnover. This prevents the release of norepinephrine, prevents D2 dopamine receptor up-regulation and augments the effects of indirect agonists.

Secondary-messengers

- Inositol Phosphate: lithium blocks the activity of inositol polyphosphate 1-phosphate and inositol monophosphate phosphatase. This leads to the depletion of inositol and dampens the function of the phosphoinositide cycle.
- Adenyl cyclase: lithium directly inhibits adenyl cyclase by competing with magnesium. Lithium also inhibits G proteins. This leads to a reduction or increase in adenyl cyclase function depending on the proportion of regional G proteins.

Pharmacokinetics

Lithium demonstrates the following pharmacokinetic properties:

Absorption

- Almost complete absorption from the gastrointestinal tract.
- Peak serum concentrations occurring 0.5 to 3 h after ingestion (standard preparations) or 4 to 4.5 h (prolonged-release preparations).

Distribution

- Does not bind to plasma proteins.
- Non-uniform distribution throughout body water.
- Does not cross the blood brain barrier rapidly.

Metabolism

- Is not catabolised in the body.

Elimination

- A half-life of approximately 24 h with steady state concentration reached after five to seven days of regular intake.
- Is eliminated, unchanged, by the kidneys.

**INDICATIONS**

Lithium is indicated in:

Prophylaxis

- Recurrent manic-depressive illness (also in schizo-affective psychosis).
- Endogenous depression.

Treatment

- Acute episodes of mania and hypomania (possibly in combination with neuroleptics).
- Certain acute depressions (e.g. in the case of resistance or intolerance to treatment with antidepressants; when transition from depression to mania suspected) possibly in combination with antidepressants.
- Acute or chronic cluster headaches (Bing-Horton syndrome).

**DOSAGE AND ADMINISTRATION**

Prolonged-release tablets:

Twice a day.

All formulations:
Dosage must be individualised according to serum concentration and clinical response. It is important to measure serum lithium concentration by taking blood samples as close as possible to 12 h after the last dose, usually 12 h after the evening dose. When switching a patient from capsules to prolonged-release tablets, the same total daily dose should be given when possible. Most patients on maintenance therapy are stabilised on 900 mg daily.

Planned Discontinuation of lithium
Gradual withdrawal of lithium (over a period of at least 2 weeks) is recommended, as it may delay recurrence of the patient's underlying symptoms. Discontinuation of lithium due to toxicity
On the first sign of toxicity, treatment should be immediately discontinued (see Warnings and Precautions, Toxicity).

Populations
- **Adults**
  - Acute Mania
    Optimal patient response can usually be established with 1800 mg per day in divided doses. Such doses will normally produce the desired serum lithium concentrations of 0.8 to 1.2 mmol/L.
  - Long-Term Therapy/Prophylaxis
    Dosage should be adjusted to maintain a serum lithium concentration of 0.5 to 1.0 mmol/L. Serum lithium concentrations should be assessed frequently during the acute phase, and in uncomplicated cases during maintenance, every two months.
  - Children
    Since information regarding the safety and efficacy in children under 12 years of age is not available, lithium therapy is not recommended in this age group.
  - Elderly
    Elderly patients often require lower lithium dosages to achieve therapeutic serum concentrations. They may also exhibit adverse reactions at serum concentrations ordinarily tolerated by younger patients (see Warnings and Precautions).

CONTRAINDICATIONS
Patients with a previous history of hypersensitivity to lithium or excipients.

WARNINGS & PRECAUTIONS
Lithium should generally not be given to patients with:
- significant renal disease
- cardiovascular disease
- untreated hypothyroidism
- sodium imbalance resulting from dehydration
- Addison's Disease
- reduced dietary salt intake
due to an increased risk of lithium toxicity. However, if the psychiatric indication is life-threatening and if such a patient fails to respond to other measures, then lithium treatment may be undertaken with extreme caution. In such cases the patient should be hospitalised and serum lithium concentrations determined daily.

Effect on the kidney
Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus with polyuria and polydipsia. Patients with the above symptoms should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Histological changes (including tubulointerstitial nephropathy) have been reported after long-term treatment with lithium. These changes may lead to impaired renal function. It is unclear if these changes are always reversible on stopping lithium. It is advisable to monitor renal function periodically.

Electroconvulsive therapy
There have been reports of increased risk of neurological adverse effects (e.g. delirium, prolonged seizures and confusion) when patients on lithium treatment received electroconvulsive therapy (ECT). If the combined treatment of lithium with ECT is clinically indicated, ECT should be used with caution and the patient should be closely monitored.

Combined therapy
Patients receiving neuroleptics concomitantly with lithium should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if symptoms appear. On extremely rare occasions, the concurrent administration of lithium with neuroleptics may result in an encephalopathic syndrome, (characterised by delirium, seizures or an increased incidence of extrapyramidal symptoms) which may be similar to or the same as neuroleptic malignant syndrome. In some instances, the syndrome was followed by irreversible brain damage.

Diuretics should only be used with caution during lithium treatment (see Interactions). Lithium concentrations should be monitored at shorter intervals and appropriate dosage adjustment should be made.

Toxicity
The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside. Lithium toxicity is closely related to serum lithium concentrations and may be expected at serum lithium concentrations equal to or above 1.5 mmol/L, although in particularly susceptible individuals they can appear at conventional therapeutic concentrations. Treatment should be discontinued immediately on the first sign of toxicity. These include:
- cardiovascular events e.g. QT/QTc prolongation
- gastrointestinal events e.g. diarrhoea, vomiting and dehydration
- neurological events e.g. ataxia, tremor, hypertonia, involuntary muscular contractions, peripheral neuropathy, hypoactive or absent deep tendon reflexes, hyperreflexia, speech disorders, confusion, somnolence and nystagmus.

Acute renal failure has been reported rarely with lithium toxicity. In severe cases convulsions, coma and death may occur (see Overdosage).

**Sodium and Potassium reabsorption**
Lithium initially decreases sodium and potassium reabsorption by the renal tubules which may lead to sodium depletion although sodium and potassium excretion should return to pre-treatment concentrations within 1 week of continuous therapy.

**OUTPATIENTS AND THEIR FAMILIES SHOULD BE WARNED**
- That the patient must contact their physician immediately if they experience clinical signs of lithium toxicity (see Toxicity above).
- Of the need for an adequate and constant salt and water intake.
- To take their medication at the stipulated time. If a dose is missed, the patient should wait until the next scheduled time of dosing. A double dose to make up for the dose that has been missed should not be taken.

The following may reduce the renal clearance of lithium and thereby precipitate intoxication:
- vomiting
- diarrhoea
- intercurrent infection
- fluid deprivation
- medications (see Interactions).

**Elderly**
Lithium should be used with particular care in the elderly since this group may be particularly susceptible to toxicity due to decreasing renal function and hence elimination (see Dosage and Administration).

Clinical worsening and suicide risk associated with depression or bipolar disorder

Patients with depression or bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. Patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

High risk patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviors or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

**Ability to perform tasks that require judgement, motor or cognitive skills**
As lithium may cause disturbances of the CNS e.g. somnolence, dizziness or hallucinations, patients should be warned of the possible hazards when driving or operating machinery.

**DRUG INTERACTIONS**
Clinicians should be aware that lithium may interact with a variety of drugs. Caution should therefore be exercised when lithium is coadministered with any other medication. In particular, the following important clinical interactions have been reported.

**Interactions which increase serum lithium concentrations**
The following have been reported to increase steady state serum lithium concentrations, possibly resulting in lithium toxicity:
- metronidazole
- non-steroidal anti-inflammatory drugs including selective cyclo-oxygenase II inhibitors
- ACE Inhibitors
- angiotensin II receptor antagonists
- diuretics (see also below):
  - thiazides, which show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication
  - potassium-sparing
  - loop.

**Interactions which decrease serum lithium concentrations**
A decrease in the serum lithium concentration may be seen on the concomitant administration of lithium with:
- urea
- xanthines
- alkalizing agents such as sodium bicarbonate
- diuretics (see also above)
  - osmotic
  - carbonic anhydrase inhibitors including acetazolamide.

Serum lithium concentrations should therefore be monitored more frequently if concomitant therapy with any of the above drugs is initiated.

**Interactions causing neurotoxicity**
The following have been reported as causing neurotoxicity (as defined by events such as ataxia, tremor, hypertonia, involuntary muscular contractions, hyperreflexia, speech disorders, confusion, somnolence and nystagmus):
- neuroleptics (see Warnings and Precautions)
- carbamazepine
- methyldopa
- selective serotonin reuptake inhibitors; concomitant administration should be undertaken with caution as this combination may precipitate a serotonergic syndrome
- calcium channel blockers; these may increase the neurotoxic effects of lithium, and serum lithium concentrations may need to be at the lower end of the therapeutic range
- tri-cyclic antidepressants.

Additional interactions
Lithium may prolong the effects of neuromuscular blocking agents.

PREGNANCY & LACTATION

Pregnancy
Human studies have identified a risk to human pregnancy or embryo-foetal development. Lithium should be avoided during pregnancy if possible, especially during the first trimester. Use of the drug near term may produce toxicity in the newborn which is usually reversible.

Lactation
Adequate human data on use during lactation and adequate animal reproduction studies are not available.

ADVERSE EFFECTS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual sensitivity to lithium and generally occur more frequently and with greater severity at higher concentrations. The margin between the therapeutic and toxic dose is narrow.

Signs of Lithium toxicity: (See Warnings and Precautions).

Initial Therapy: Fine hand tremor, polyuria, thirst and nausea may occur during initial therapy. These effects usually subside with continued therapy or with dose reduction. The following reactions appear to be related to serum lithium concentrations within the therapeutic range. The frequency classifications for these adverse reactions cannot be accurately estimated from the available clinical trial data.

Blood and lymphatic system disorders: Leukocytosis

Endocrine disorders: Euthyroid goitre, hypothyroidism, hyperthyroidism, hyperparathyroidism

Metabolism and nutrition disorders: Hyperglycemia, hypercalcemia, weight gain, anorexia

Psychiatric disorders: Hallucinations, somnolence, memory loss

Nervous system disorders: Tremor, fasciculations / twitching, clonic movements of extremities, ataxia, choreoathetoid movements, impaired nerve conduction, hyperactive deep tendon reflexes, extrapyramidal symptoms, seizures, slurred speech, dizziness, vertigo, nystagmus, stupor, coma, pseudotumor cerebri, headache, dysgeusia, myasthenia gravis

Eye disorders: Scotomata, blurred vision

Cardiac disorders: Cardiac arrhythmia, of which bradycardia due to sinus node dysfunction is most frequent, and oedema. ECG changes: reversible flattening and inversion of T-waves.

Vascular disorders: Peripheral circulatory collapse, hypotension, Raynaud's phenomena

Gastrointestinal disorders: Nausea, vomiting, diarrhoea, gastritis, excessive salivation, dry mouth

Skin and subcutaneous tissue disorders: Alopecia, acne, folliculitis, pruritus, psoriasis exacerbation, angioedema, rash and other signs of skin hypersensitivity

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia

Renal and urinary disorders: Symptoms of nephrogenic diabetes insipidus, urinary incontinence, and after long-term therapy, histological renal changes (including tubulointerstitial nephropathy) and impaired renal function

Reproductive system and breast disorders: Impotence, sexual dysfunction

General disorders and administration site conditions: Oedema
OVERDOSAGE AND TREATMENT

The toxic concentrations for lithium are close to the therapeutic concentrations. Any overdose with lithium should be regarded as potentially serious. For patients on chronic lithium therapy even a modest overdose can lead to serious toxicity as the extravascular tissues are already saturated with lithium.

Symptoms and Signs
See Warnings and Precautions.

The onset of symptoms may be delayed, with peak effects not occurring for as long as 24 h, especially in patients who are not receiving chronic lithium therapy or following the use of a prolonged-release preparation. Symptoms are similar to those described in the Adverse Effects section. In severe cases seizure, coma and death may ensue.

Treatment
There is no known antidote. Supportive and symptomatic treatment should be initiated. Correction of electrolyte balance and fluid resuscitation is critical.

Whole bowel irrigation has been reported to be helpful in patients ingesting large quantities of prolonged-release preparation.

Haemodialysis is an effective treatment for severe lithium poisoning and should be considered in all patients with marked neurological features. Substantial rebound increases in serum lithium concentrations can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Haemodialysis should be considered in patients with severe symptoms regardless of serum lithium concentration.

Serum lithium levels should be monitored. Clinical improvement generally takes longer than reduction of serum lithium concentrations.

Activated charcoal does not adsorb lithium.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

STORAGE CONDITIONS
Store at a temperature not exceeding 30°C

AVAILABILITY
Lithium carbonate (Quilonium®) 450mg Prolonged-release Tablet: Plastic bottle by 250’s

CAUTION
Foods, Drugs Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

QUILONIUM-R is a registered trademark of the GlaxoSmithKline group of companies. ©2010, GlaxoSmithKline. All rights reserved.

Version number: GDS17 Revision Date: 24 June 2010

Imported by:
GlaxoSmithKline Philippines Inc.
2266 Chino Roces Avenue, City of Makati
Tel no. 892-0761

Mfd by:
Haupt Pharma Wölfing GmbH
Gronau, Germany

Packed by:
SmithKline Beecham
Gainta, Rizal