

New Zealand Data Sheet



1. PRODUCT NAME

Lithium Carbonate 250mg Capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Lithium Carbonate capsule contains 250mg of lithium carbonate.

Excipient(s) with known effect

Lithium Carbonate capsules contain lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Size one capsule with a clear body and a green cap containing white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of mania and hypomania.
- Treatment of some patients with recurrent bipolar depression, for which treatment with other antidepressants have been unsuccessful.
- Prophylactic treatment of recurrent affective disorders.

4.2. Dose and method of administration

Dose

A simple treatment schedule has been evolved which, except for some minor variations, should be followed whether using Lithium Carbonate therapeutically or prophylactically. The minor variations to this schedule depend on the elements of the illness being treated and these are described later.

1. In patients of average weight (70kg) an initial dose of 400-1,200mg of Lithium Carbonate may be given as a single daily dose in the morning or on retiring. Alternatively, the dose may be divided and given morning and evening. When changing from other lithium preparations serum lithium levels should first be checked, then Lithium Carbonate therapy commenced at a daily dose as close as possible to the dose of the other form of lithium. As bioavailability varies from product to product (particularly with regard to retard or slow release preparations), a change of product should be regarded as initiation of new treatment.

2. Four to five days after starting treatment (and never longer than one week) a blood sample should be taken for the estimation of serum lithium level.
3. The objective is to adjust the Lithium carbonate dose so as to maintain the serum lithium level permanently within the diurnal range of 0.5 – 1.5 mmol/L. In practice, the blood sample should be taken between 12 and 24 hours after the previous dose of Lithium carbonate. 'Target' serum lithium concentrations at 12 and 24 hours are shown in Table 1. Serum lithium levels should be monitored weekly until stabilisation is achieved.

Table 1: 'Target' serum lithium concentrations (mmol/L)

	At 12 hours	At 24 hours
Once daily dosage	0.7 – 1.0	0.5 – 0.8
Twice daily dosage	0.5 – 0.8	

4. Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. Following stabilisation of serum lithium levels, the period between subsequent estimations can be increased gradually but should not normally exceed three months. Additional measurements should be made following alteration of dosage, on development of intercurrent disease, signs of manic or depressive relapse, following significant change in sodium or fluid intake, or if signs of lithium toxicity occur.
5. Whilst a high proportion of acutely ill patients may respond within three to seven days of the commencement of Lithium carbonate therapy, Lithium carbonate should be continued through any recurrence of the affective disturbance. This is important as the full prophylactic effect may not occur for 6 to 12 months after the initiation of therapy.
6. In patients who show a positive response to Lithium Carbonate therapy, treatment is likely to be long term. Careful clinical appraisal of the patient should be exercised throughout medication (see section 6.6).

Treatment of Acute Mania, Hypomania and Recurrent Bipolar Depression

It is likely that a higher than normal Lithium Carbonate intake may be necessary during an acute phase and divided doses would be required here. Therefore, as soon as control of mania or depression is achieved, the serum lithium level should be determined and it may be necessary, dependent on the results, to lower the dose of Lithium Carbonate and re-stabilise serum lithium levels. In all other details the described treatment schedule is recommended.

Prophylactic Treatment of Recurrent Affective Disorders

It is recommended that the described treatment schedule is followed.

Elderly Population

In elderly patients or those below 50kg in weight, it is recommended that the starting dose be 400mg. Elderly patients may be more sensitive to undesirable effects of lithium and may also require lower doses in order to maintain normal serum lithium levels. It follows therefore that long term patients often require a reduction in dosage over a period of years.

Children and Adolescents

Not recommended.

Renal impairment

Lithium is contraindicated in patients with significant renal disease (see Section 4.3).

Method of Administration

Lithium should be taken with food, as it causes less nausea than on an empty stomach.

4.3. Contraindications

- Patients with significant cardiovascular disease
- Patients with significant renal disease
- Untreated hypothyroidism
- Conditions associated with hyponatremia, for example: Addison's disease, dehydrated or severely debilitated patients, patients on low sodium diets
- Diuretics should not be used during lithium therapy without appropriate dosage adjustment
- Hypersensitivity to lithium or any of the excipients contained in the capsule
- Breastfeeding

4.4. Special warnings and precautions for use

General

When considering lithium therapy, it is necessary to ascertain whether patients are receiving lithium in any other form. If so, check serum levels before proceeding.

Patients receiving lithium therapy should be taught to recognise the symptoms of early toxicity and, should these occur, to discontinue therapy and request medical aid at once (see section 4.9).

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. For monitoring recommendations of lithium serum levels (see section 4.2).

Monitoring recommendations

Pre-treatment

Physical examination and laboratory testing are required prior to commencement of therapy and should be repeated at frequent intervals.

Since lithium is excreted primarily by the kidney, adequate renal function is essential in order to avoid lithium accumulation and intoxication. If necessary, a creatinine clearance test or other renal function test should be performed.

Cardiac, thyroid and parathyroid (parathyroid hormone and serum calcium level) function should be assessed before commencing lithium treatment. Thus, a decision to initiate lithium therapy should be preceded by a thorough clinical examination and evaluation of each patient, including laboratory determinations, ECG, and a very careful assessment of renal function.

On treatment

Patients receiving lithium should be examined periodically for abnormal thyroid and parathyroid function (see section 4.4), since goitre and hypothyroidism may develop. Cardiac and renal function should be monitored regularly. Care should be taken in the presence of encephalopathy syndrome or intercurrent infection.

Patients should be maintained under careful clinical and laboratory control throughout treatment. Means of obtaining accurate determination of serum lithium levels should be available since frequent serum determinations are required during the initial period of treatment.

Renal impairment

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have also been reported in patients on chronic lithium therapy. Some structural changes have also been reported in manic-depressives never exposed to lithium. The relationship between renal function, morphologic changes and lithium therapy has not been established. When kidney function is assessed, routine urinalysis and other tests may be used to evaluate tubular function (e.g. urine specific gravity, osmolality following water deprivation or 24-hour urine volume) and glomerular function (e.g. serum creatinine or creatinine clearance). Of note, acute renal failure has been reported rarely with lithium toxicity.

Fluid/electrolyte balance

Vomiting, diarrhoea, intercurrent infection, fluid deprivation and drugs likely to upset electrolyte balance, such as diuretics, may all reduce lithium excretion thereby precipitating intoxication. Therefore, reduction in the dosage of lithium may be required. Lithium requirements may change during fever, infection, and when mood swings occur. Patients in a manic state seem to have increased tolerance to lithium which decreases when manic symptoms subside.

Patients should avoid low-salt dietary regimens or other dietary changes which may reduce sodium intake, or circumstances which may cause excessive sodium loss such as heavy exercise leading to excessive sweating as these may lead to increased lithium concentrations.

The patient, therefore, should maintain a normal diet with adequate salt and fluid intake during therapy.

Hypercalcaemia and Hyperparathyroidism

Systematic review indicates that about 10 % of patients taking lithium long-term develop hypercalcaemia with or without hyperparathyroidism. Patients should be checked for parathyroid function prior to commencing treatment.

Serum calcium levels should be monitored at least yearly in all patients taking lithium. Monitoring should be more frequent if an abnormal result is found or the patient has a family history of endocrine disease. If serum calcium levels are raised the serum parathyroid level should be measured. If both parathyroid hormone levels and calcium levels are elevated the patient should be referred for specialist treatment.

In cases of mild hypercalcaemia with normal parathyroid hormone levels treatment may be continued if the benefits are considered to outweigh the risks, but calcium levels should be monitored more frequently.

If serum calcium levels rise above 11 mg/dL lithium treatment should be stopped and calcium levels measured weekly for the next 4 weeks to ensure that levels drop back to normal.

Patients who have undergone parathyroidectomy in the past may experience recurrent hyperparathyroidism on lithium treatment; serum calcium and parathyroid hormone levels should be carefully monitored.

Electroconvulsive therapy

Lithium should be temporarily discontinued before electroconvulsive therapy (ECT) to reduce the risk of delirium, which may occur when the two treatments are co-administered.

Surgery

It is wise to discontinue lithium for 24 hours before any major operation. Provided serum electrolytes are in balance it can, and normally should, be restarted soon after the operation. Complete discontinuation of prophylactic lithium therapy should be discussed between patient, general practitioner and specialist.

Children

Information regarding the safety and efficacy in children under 12 years of age is not available, therefore lithium therapy is not recommended in this age group.

Elderly patients

Lithium should be used with care in the elderly as excretion may be reduced, resulting in a longer half-life. The elderly may, therefore, exhibit signs of toxicity at serum concentrations ordinarily tolerated by younger patients. Elderly patients also often require lower lithium dosages to achieve therapeutic serum concentrations.

4.5. Interaction with other medicines and other forms of interaction

If one of the following medicines is initiated, regular monitoring of serum lithium levels and for signs of lithium toxicity should be performed during concomitant treatment. Lithium dosage should either be adjusted, or concomitant treatment stopped, as appropriate.

Interactions that may increase lithium concentrations

- Selective Serotonin Re-uptake Inhibitors (SSRIs)
- Metronidazole
- Tetracyclines
- Non-steroidal anti-inflammatory drugs (NSAID)
- ACE inhibitors
- Thiazide diuretics (may cause a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication)
- Spironolactone
- Frusemide
- Angiotensin-II receptor antagonists
- Other drugs affecting electrolyte balance may alter lithium excretion, e.g. steroids

Interactions that may decrease lithium concentration

- Xanthines (theophylline, caffeine)
- Sodium bicarbonate and Sodium Chloride containing products
- Psyllium or Ispaghula husk
- Urea
- Mannitol
- Acetazolamide

Interactions that may cause neurotoxicity

- Neuroleptics (risperidone, clozapine, phenothiazines, and particularly haloperidol) may lead to, in rare cases, neurotoxicity in the form of an encephalopathic syndrome, characterised by weakness, lethargy, fever, tremulousness, confusion, extrapyramidal symptoms and leucocytosis. In some instances, the syndrome was followed by irreversible brain damage. Because there is a possible causal relationship between these events and treatment with lithium and neuroleptics, patients receiving combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if symptoms appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome.

- SSRIs, Sumatriptan and Tricyclic Antidepressants have been associated with episodes of neurotoxicity and may precipitate a serotonergic syndrome - either event justifies immediate discontinuation of treatment.
- Calcium channel blockers may lead to a risk of neurotoxicity in the form of ataxia, confusion and somnolence, reversible after discontinuation of the drug. Lithium concentrations may be increased or decreased.
- Carbamazepine or phenytoin may lead to dizziness, somnolence, confusion and cerebellar symptoms.
- Methyldopa

Other interactions

- Lithium may prolong the effects of neuromuscular blocking agents
- Thioridazine may increase risk of ventricular dysrhythmias
- Iodide and lithium may act synergistically to produce hypothyroidism
- There have also been case reports of lithium interactions with baclofen, co-trimoxazole, aciclovir and prostaglandin-synthetase inhibitors. The clinical significance of these interactions is uncertain.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraception throughout lithium treatment should be considered and a joint decision between prescriber and patient should be made when considering continuation of lithium treatment in pregnancy.

Pregnancy

It is strongly recommended that lithium be discontinued before a planned pregnancy as the risk of birth defects may be increased when lithium is used during the first trimester. Therefore, the potential benefits of continued administration during pregnancy must be weighed against the possible adverse effects. Lithium crosses the placental barrier (see section 5.2).

There is epidemiological evidence that lithium may be harmful to the foetus in human pregnancy. Cardiac effects, especially Ebstein's anomaly, and other malformation have been reported (see table below).

Total no. "lithium babies" reported	Malformed infants	Ebstein's anomaly and other major cardio-vascular malformations
225	25 (11%)	18 (8%)

The absolute risk for infant cardiac malformation after exposure to lithium during the first trimester in the study by Patorno et al¹ (2.4%) was similar to the absolute risk in the Munk-Olsen study² (2.1%). A pre-natal diagnosis, such as ultrasound and electrocardiogram examination, is strongly recommended.

In certain cases where a severe risk to the patient could exist if treatment were stopped, lithium has been continued during pregnancy. If it is considered essential to maintain Lithium Carbonate treatment during pregnancy, serum lithium levels should be monitored closely since renal function changes gradually during pregnancy and suddenly at parturition, requiring dosage adjustments. It is recommended that lithium be discontinued shortly before delivery and recommenced a few days post-partum.

Neonates may show signs of lithium toxicity including symptoms such as lethargy, flaccid muscle tone, hypotonia. Neonates showing signs of lithium intoxication may require fluid therapy in the neonatal period. Babies born with low serum lithium concentrations may have a flaccid appearance which returns to without any treatment. Careful clinical observation of the neonate exposed to lithium during pregnancy is recommended and lithium levels may need to be monitored as necessary.

Breast-feeding

Lithium should not be used during breast-feeding (see section 4.3). Lithium is excreted in breast milk, therefore bottle feeding is recommended. There have been case reports of neonates showing signs of lithium toxicity.

Fertility

See section 5.3.

4.7. Effects on ability to drive and use machines

Lithium may cause disturbances of the central nervous system (e.g. somnolence, dizziness, and hallucinations). Furthermore, at the beginning of treatment the occasional onset of fatigue can impair reflexes. Therefore, Impaired driving performance or machine operation skills may occur in patients receiving lithium.

4.8. Undesirable 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.

¹ Patorno E et al. The New England journal of medicine. 2017 Aug 31;377(9):893-4

² Munk-Olsen T et al. The Lancet Psychiatry. 2018 Aug;5(8):644-52

The most frequent adverse effects are the initial post-absorptive symptoms, believed to be associated with a rapid rise in serum lithium levels. They include gastrointestinal discomfort with mild nausea and diarrhoea, vertigo, muscle weakness and a dazed feeling and frequently disappear after stabilisation of therapy.

The more common and persistent adverse reactions are fine tremor of the hands, fatigue, thirst and polyuria. These do not necessarily require reduction of dosage. Nausea is usually transient

Adverse effects occurring at therapeutic serum lithium concentrations include anorexia, constipation or diarrhoea, epigastric discomfort, metallic taste, headache, vertigo, fine tremor, polyuria with polydipsia, and oedema. Hypercalcaemia has been reported in about 10 % of patients taking lithium, hypermagnesaemia and hyperparathyroidism have also been reported. Reversible ECG changes e.g. T wave flattening, or inversion, cardiac arrhythmias and EEG changes have been reported. Exacerbation of skin conditions (such as acne and psoriasis) and leucocytosis are relatively common side-effects of lithium therapy. Significant weight gain is also observed in many patients receiving lithium.

Long term administration of lithium carbonate may precipitate goitre requiring treatment with thyroxine, but this regresses when treatment is discontinued. Hair thinning and mild cognitive impairment may occur. Rarely hyperthyroidism, hyperparathyroidism and nephrogenic diabetes insipidus have been reported.

Toxic effects may be expected at serum-lithium concentrations over 1.5 mmol/L, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously. Signs of toxicity include increasing diarrhoea, vomiting, anorexia, severe abdominal discomfort, polyuria, muscle weakness, lethargy, ataxia, lack of co-ordination, tinnitus, blurred vision, dry mouth, dysgeusia and impotence/sexual dysfunction, coarse tremor (marked) of the extremities and lower jaw, muscle hyperirritability and twitching, agitation, hyper-reflexia, choreoathetoid movements, dysarthria, disorientation, psychosis, drowsiness, seizures and coma. At higher concentrations, ataxia, tinnitus, blurred vision, giddiness and increasing polyuria are seen.

The following reactions appear to be related to serum lithium concentrations. Adverse reactions can occur in patients with serum concentrations within the therapeutic range (i.e. below 1.5 mmol/L or lower in the elderly).

- Body as a whole: Oedema
- Cardiovascular: Arrhythmia, hypotension, ECG changes including non-specific T wave changes, oedema, Raynaud's phenomena, peripheral circulatory collapse, bradycardia, sinus node dysfunction.
- Dermatological: Alopecia, acne, folliculitis, pruritus, psoriasis exacerbation, rash.
- Endocrine: Euthyroid goitre, hypothyroidism, rare cases of hyperthyroidism, hyperglycaemia, hypercalcaemia, hypermagnesemia, hyperparathyroidism.

- Gastrointestinal: Anorexia, nausea, vomiting, diarrhoea, constipation, gastritis, excessive salivation, abdominal pain.
- Haematological: Leucocytosis.
- Hypersensitivity: Angioedema.
- Neuromuscular/CNS: Tremor, fasciculations, twitching clonic movements of extremities, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes, extrapyramidal symptoms, syncope, seizures, slurred speech, dizziness, vertigo, nystagmus, somnolence, stupor, coma, hallucinations, taste distortion, taste impairment, scotomata, pseudotumour cerebri, autonomic effects including blurred vision, dry mouth, impotence/sexual dysfunction, headache and EEG changes. Myasthenia gravis has been observed rarely.
- Renal: Symptoms of nephrogenic diabetes insipidus.

It is vital to bear in mind that lithium can be lethal, if prescribed or ingested in excess.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

In acute overdose, vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a latency period and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdose are reported to be mainly related to the alimentary and nervous systems and include abdominal pain, anorexia, nausea, vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, depression, renal symptoms.

Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

Treatment

Treatment is symptomatic and supportive; close monitoring of vital signs is recommended. Activated charcoal is of no value as it does not adsorb lithium. Whole bowel irrigation has been suggested, however, there are no clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured, and any electrolyte imbalance corrected but forced diuresis or diuretics should not be used (see Section 4.5). Appropriate supportive care

may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Lithium ATC code: N05AN01

Mechanism of action

Lithium Carbonate provides a source of lithium ions that may act by competing with sodium ions at various sites in the body. Therapeutic concentrations of lithium have almost no discernible psychotropic effects in normal volunteers but considerable effect in patients suffering from affective disorders. The mechanism of action is unknown.

5.2. Pharmacokinetic properties

Absorption

Lithium ions are almost completely absorbed from the gastrointestinal tract, complete absorption occurring after about 8 hours. Peak plasma concentrations occur after about 2-4 hours.

Distribution

Lithium initially distributes into extracellular fluid and then to most other tissues. The final volume of distribution equals that of total body water. Lithium slowly enters cerebrospinal fluid achieving at steady state 40% of the plasma concentration. Lithium is able to cross the placenta and is excreted in breast milk.

Elimination

Occurs via the kidneys but lithium can also be detected in sweat and saliva. The biological half-life is variable ranging from 7-20 hours and may be longer at night. Poor renal function impairs excretion.

Special populations

Elimination half-life may be increased in elderly patients due to age related decrease in renal function and also in patients with renal impairment (see sections 4.2 and 4.4).

5.3. Preclinical safety data

In animal studies, lithium has been reported to interfere with fertility, gestation and foetal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lithium Carbonate Capsules contains lactose monohydrate, maize starch, magnesium stearate, gelatin, EEC Quinoline Yellow E104, FD&C Blue #1 E133 and FD&C Yellow # E110

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

Lithium Carbonate 250mg Capsules: Bottle, plastic, HDPE, 100 capsules.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

8 November 1985

10. DATE OF REVISION OF THE TEXT

28 March 2019

Summary table of changes

Section Changed	Summary of new information
All	Formatting changes as per new template.
2, 3, 6.3	Minor corrections as per new template.
4.6	Additional information as per recommendations from MARC on potential risks following foetal exposure to lithium during pregnancy.