

NEW ZEALAND DATA SHEET

LITHICARB FC

Lithium carbonate Tablets 250mg and 400mg



Presentation

LITHICARB 250mg tablets are clear film coated, white biconvex tablets, 11.1 mm diameter, imprinted "LC" breakline over "250" on one side. Each tablet contains 250 mg of the active ingredient, lithium carbonate.

LITHICARB 400mg tablets are clear film coated, white biconvex tablets, 12.7 mm diameter, imprinted "LC" breakline over "400" on one side. Each tablet contains 400 mg of the active ingredient, lithium carbonate.

Uses

Actions

Lithium carbonate is used as a source of lithium ions, which may act by competing with sodium ions at various sites. It causes changes in the composition of electrolytes in body fluids and increases the intracellular and total body water volume. The mechanism by which it exerts its effect in affective disorders is not known.

Pharmacokinetics

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts. Peak serum concentrations are obtained between 0.5 and 3 hours after ingestion from conventional tablets. Lithium is distributed throughout the body and distribution is complete within about 6 to 10 hours with higher concentrations occurring in the bones, the thyroid gland, and portions of the brain, than in the serum.

Lithium is excreted mainly in the urine and is not bound to plasma proteins.

The elimination half-life has been reported to range from about 10 to 50 hours but in patients with normal renal function the average is about 20 to 24 hours. This means that about one week may elapse after the initiation of treatment before steady-state concentrations are attained.

Lithium crosses the placenta and is excreted in breast milk.

Indications

1. Treatment of mania and hypomania.
 2. Lithium may also be tried in the treatment of some patients with recurrent bipolar depression, for which treatment with other antidepressants has been unsuccessful.
 3. Prophylactic treatment of recurrent affective disorders.
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Dosage and Administration

It is advisable to take LITHICARB FC with food as it causes less nausea than on an empty stomach.

A simple treatment schedule has been evolved which, except for some minor variations, should be followed whether using LITHICARB FC 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 400-1,200 mg of LITHICARB FC may be given as a single daily dose in the morning or on retiring. Alternatively, the dose may be divided and given morning
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and evening. The tablets should not be crushed, chewed or swallowed with hot liquids. When changing from other lithium preparations serum lithium levels should first be checked, then LITHICARB FC 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 LITHICARB FC 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 LITHICARB FC. 'Target' serum lithium concentrations at 12 and 24 hours are shown in Table 1.

LITHICARB FC tablets are scored, therefore they can be divided accurately to provide dosage adjustments as small as 125mg. Serum lithium levels should be monitored weekly until stabilisation is achieved.

Table 1. Target serum lithium concentrations

	"Target" serum lithium concentration (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 LITHICARB FC therapy, LITHICARB FC 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 LITHICARB FC therapy, treatment is likely to be long term. Careful clinical appraisal of the patient should be exercised throughout medication (see Precautions).

Treatment of Acute Mania, Hypomania and Recurrent Bipolar Depression

It is likely that a higher than normal LITHICARB FC 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 LITHICARB FC 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.

Use in the Elderly

In elderly patients or those below 50 kg in weight, it is recommended that the starting dose be 400 mg. 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.

Use in Children and Adolescents

Not recommended.

Contraindications

Lithium carbonate is contra-indicated in the following conditions:-

- Patients with significant cardiovascular or renal disease
 - Conditions associated with hyponatraemia such as Addison's disease, dehydrated or severely debilitated patients, and patients on low sodium diets
 - Known hypersensitivity to lithium or to any of the excipients in LITHICARB FC tablets
 - Breastfeeding
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Warnings and Precautions

Monitoring Requirements

When considering LITHICARB FC therapy, it is necessary to ascertain whether patients are receiving lithium in any other form. If so, check serum levels before proceeding. It is important to ensure that renal function is normal - if necessary a creatinine clearance test or other renal function test should be performed. Cardiac and thyroid function should be assessed before commencing lithium treatment. Patients should be euthyroid before the initiation of lithium therapy. Renal function, cardiac function and thyroid function should be reassessed periodically. Care should be taken in the presence of Encephalopathic syndrome or intercurrent infection.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long term lithium therapy (see Lithium toxicity). Patients should also be warned to report if polyuria or polydipsia develop. Episodes of nausea and vomiting or other conditions leading to salt/water depletion (including severe dieting) should also be reported. Elderly patients are particularly liable to lithium toxicity.

Caution should be exercised to ensure that diet and fluid intake are normal, thus maintaining a stable electrolyte balance. This may be of special importance in very hot weather or work environment. Infectious diseases including colds, influenza, gastroenteritis and urinary infections may alter fluid balance and thus affect serum lithium levels. Treatment should be discontinued during any intercurrent infection and should only be reinstated after the patient's physical health has returned to normal.

Lithium toxicity

Patients and family members should be warned of the signs and symptoms of impending lithium intoxication such as:

1. Gastro-Intestinal
Increasing anorexia, diarrhoea and vomiting.
2. Central Nervous System
Muscle weakness, lack of co-ordination, drowsiness or lethargy progressing to giddiness and ataxia, tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching.

At blood levels above 2-3 mmol/L there may be a large output of dilute urine, with increasing disorientation, seizures, coma and death.

If toxic symptoms appear, patients should be instructed to immediately stop taking LITHICARB FC and to report for a serum lithium estimation.

Monitoring Requirements

As described under Dosage and Administration, monitoring of lithium levels should include pre-treatment testing and ongoing clinical and laboratory evaluations. Monitoring frequency should be increased when the dosage is changed, if the patient is unwell, or if signs of lithium toxicity develop.

Renal impairment/nephrotoxicity

Up to one third of patients on lithium may develop nephrogenic diabetes insipidus, characterised by polyuria, polydipsia and a urinary output of up to three litres per day. This is usually due to lithium blocking the effect of ADH and is reversible on lithium withdrawal.

However, long term treatment with lithium may also result in permanent changes in kidney histology and impairment of renal function. High serum concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes.

The minimum clinically effective dose of lithium should always be used.

Renal function should be monitored in all patients not just those with polyuria or polydipsia, e.g. with measurement of blood urea, serum creatinine and urinary protein levels in addition to the routine serum lithium estimations. Patients should be instructed to report any symptoms of polyuria, polydipsia, nausea or vomiting.

Elderly

Elderly patients are at a greater risk of lithium toxicity. Lithium should be used with care in the elderly, as excretion may be reduced, half-life increased, and signs of toxicity can occur at serum concentrations ordinarily tolerated by younger patients. Elderly patients often require lower dosages to achieve therapeutic serum concentrations.

Pregnancy and Lactation

There is epidemiological evidence that lithium may be harmful to the foetus in human pregnancy.

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

It is strongly recommended that lithium be discontinued before a planned pregnancy. If it is considered essential to maintain LITHICARB FC 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.

Babies may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Babies born with low serum lithium concentrations may have a flaccid appearance which returns to normal without any treatment. Lithium is secreted in breast milk, therefore bottle feeding is recommended.

Interactions

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
- Topiramate
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- ACE inhibitors
- Thiazide diuretics (may cause a paradoxical anti-diuretic 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 concentrations

- 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 confusion, disorientation, lethargy, tremor, extra-pyramidal symptoms and myoclonus
- SSRIs, sumatriptan and tricyclic antidepressants have been associated with episodes of neurotoxicity, and may precipitate a serotoninergic 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
- Methyl dopa.

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, cotrimoxazole, acyclovir and prostaglandin-synthetase inhibitors. The clinical significance of these interactions is uncertain.

Adverse Effects

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol/L.

Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur initially, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist. Weight gain or oedema may present in some patients but should not be treated with diuretics.

Hypercalcaemia, hypermagnesaemia and hyperparathyroidism have been reported. Skin conditions including acne, psoriasis, generalised pustular psoriasis, rashes and leg ulcers have occasionally been reported as being aggravated by lithium treatment.

Long term treatment with lithium may be associated with disturbances of thyroid function, including goitre, hypothyroidism and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine.

Memory impairment may occur during long term use.

After a period lasting 3-5 years, patients should be carefully assessed to ensure that benefit persists.

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. Cardia 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, hyperparathyroidism, weight gain.

Gastrointestinal. Anorexia, nausea, vomiting, diarrhoea, 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, dysgeusia and impotence/sexual dysfunction. Myasthenia gravis has been observed rarely.

Renal. Symptoms of nephrogenic diabetes insipidus.

Overdosage

Symptoms

In acute overdosage, 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 overdosage 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; recommend closely monitoring vital signs. Activated charcoal is of no value. Whole bowel irrigation has been suggested although there do not appear to be 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 are contraindicated. 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.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

LITHICARB 250mg Tablets: Bottles of 100 (not currently marketed) and 500 tablets.
LITHICARB 400mg Tablets: Bottles of 100 tablets.

Further Information

LITHICARB FC tablets contain the following ingredients in addition to the active ingredient: lactose, maize starch, povidone, sodium starch glycollate magnesium stearate, carbuba wax, hypromellose and diethyl phthalate

Name and Address

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone: 09-579-2792

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