Summary of Product Characteristics

1. Name of the medicinal product
Lithium Carbonate Extended-Release Tablets USP 450 mg

2. Qualitative and quantitative composition
Each Extended-Release Film Coated Tablet contains:
Lithium Carbonate USP……450 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Extended-Release Tablets.

4. Clinical particulars
4.1 Therapeutic indications
Lithium Carbonate Extended-Release Tablets are indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.
Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness and possibly hostility. When given to a patient experiencing a manic episode, Lithium Carbonate Extended-Release Tablets may produce a normalization of symptomatology within 1 to 3 weeks.

4.2 Posology and method of administration
Doses of controlled-release tablets are usually given b.i.d. (approximately 12-hour intervals). When initiating therapy with controlled-release lithium, dosage must be individualized according to serum levels and clinical response.
When switching a patient from immediate-release capsules to Lithium Carbonate Extended-Release Tablets, give the same total daily dose when possible. Most patients on maintenance therapy are stabilized on 900 mg daily, e.g., Lithium Carbonate Extended-Release Tablets 450 mg b.i.d. When the previous dosage of immediate-release lithium is not a multiple of 450 mg, e.g., 1,500 mg, initiate Lithium Carbonate Extended-Release Tablets at the multiple of 450 mg nearest to, but below, the original daily dose, i.e., 1,350 mg. When the 2 doses are unequal, give the larger dose in the evening. In the above example, with a total daily dose of 1,350 mg, generally 450 mg of Lithium Carbonate Extended-Release Tablets should be given in the morning and 900 mg of Lithium Carbonate Extended-Release Tablets in the evening. If desired, the total daily dose of 1,350 mg can be given in 3 equal 450-mg doses of Lithium Carbonate Extended-Release Tablets. These patients should be monitored at 1- to 2-week intervals, and dosage adjusted if necessary, until stable and satisfactory serum levels and clinical state are achieved.
When patients require closer titration than that available with doses of Lithium Carbonate Extended-Release Tablets in increments of 450 mg, immediate-release capsules should be used.
Acute Mania: Optimal patient response to Lithium Carbonate Extended-Release Tablets can usually be established and maintained with 1,800 mg per day in divided doses. Such doses will normally produce the desired serum lithium level ranging between 1 and 1.5 mEq/L.
Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

Long-Term Control: The desirable serum lithium levels are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually 900 mg to 1,200 mg per day in divided doses will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months.

Patients unusually sensitive to lithium may exhibit toxic signs at serum levels below 1 mEq/L.

Important Considerations

• Blood samples for serum lithium determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e., 8 to 12 hours after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

• Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by younger patients.

• Lithium Carbonate Extended-Release Tablets must be swallowed whole and never chewed or crushed.

Pediatric Use

Safety and effectiveness in pediatric patients under 12 years of age have not been determined; its use in these patients is not recommended.

There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

Geriatric Use

Clinical studies of Lithium Carbonate Extended-Release Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed.
• Cardiac disease.
• Cardiac insufficiency.
• Severe renal impairment.
• Untreated hypothyroidism.
• Breast-feeding.
• Patients with low body sodium levels, including for example dehydrated patients or those on low sodium diets.
• Addison's disease.
• Brugada syndrome or family history of Brugada syndrome.

4.4 Special warnings and precautions for use

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

Lithium Toxicity

The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic range (0.8 to 1.2 mEq/L). Some patients abnormally sensitive to lithium may exhibit toxic signs at serum concentrations that are considered within the therapeutic range. Lithium may take up to 24 hours to distribute into brain tissue, so occurrence of acute toxicity symptoms may be delayed.

Neurological signs of lithium toxicity range from mild neurological adverse reactions such as fine tremor, lightheadedness, lack of coordination, and weakness; to moderate manifestations like giddiness, apathy, drowsiness, hyperreflexia, muscle twitching, ataxia, blurred vision, tinnitus, and slurred speech; and severe manifestations such as clonus, confusion, seizure, coma, and death. In rare cases, neurological sequelae may persist despite discontinuing lithium treatment and may be associated with cerebellar atrophy. Cardiac manifestations involve electrocardiographic changes, such as prolonged QT interval, ST and T-wave changes and myocarditis. Renal manifestations include urine concentrating defect, nephrogenic diabetes insipidus, and renal failure. Respiratory manifestations include dyspnea, aspiration pneumonia, and respiratory failure. Gastrointestinal manifestations include nausea, vomiting, diarrhea, and bloating. No specific antidote for lithium poisoning is known.

The risk of lithium toxicity is increased by:

• Recent onset of concurrent febrile illness

• Concomitant administration of drugs which increase lithium serum concentrations by pharmacokinetic interactions or drugs affecting kidney function.

• Acute ingestion

• Impaired renal function

• Volume depletion or dehydration

• Significant cardiovascular disease

• Changes in electrolyte concentrations (especially sodium and potassium)

Monitor for signs and symptoms of lithium toxicity. If symptoms occur, decrease dosage or discontinue lithium treatment.

Unmasking of Brugada Syndrome

There have been postmarketing reports of a possible association between treatment with lithium and the unmasking of Brugada Syndrome. Brugada Syndrome is a disorder characterized by abnormal electrocardiographic (ECG) findings and a risk of sudden death. Lithium should generally be avoided in patients with Brugada Syndrome or those suspected of having Brugada Syndrome. Consultation with a cardiologist is recommended if: (1) treatment with lithium is under consideration for patients suspected of having Brugada Syndrome or patients who have risk factors for Brugada Syndrome, e.g., unexplained syncope, a family history of Brugada Syndrome, or a family history of sudden unexplained death before the age of 45 years, (2) patients who develop unexplained syncope or palpitations after starting lithium therapy.

Pseudotumor Cerebri

Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields, and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

Renal Effects

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.

Post marketing cases consistent with nephrotic syndrome have been reported with the use of lithium. Biopsy findings in patients with nephrotic syndrome include minimal change disease and focal segmental glomerulosclerosis. Discontinuation of lithium in patients with nephrotic syndrome has resulted in remission of nephrotic syndrome.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. Routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine, creatinine clearance or proteinuria). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

Encephalopathic Syndrome

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

Serotonin Syndrome

Lithium can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, triptans, tricyclic antidepressants, fentanyl, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Monitor all patients taking lithium for the emergence of serotonin syndrome. Discontinue treatment with lithium and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of lithium with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

Concomitant Use with Neuromuscular Blocking Agents

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

PRECAUTIONS

General
The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside.
The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-life of elimination of lithium is approximately 24 hours.
Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2,500 to 3,000 mL) at least during the initial stabilization period.
Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.
In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.
Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; where hypothyroidism pre-exists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters, if any; where hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.
Information for Patients
Lithium carbonate may impair mental and/or physical abilities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).
A condition known as Brugada Syndrome may pre-exist and be unmasked by lithium therapy. Brugada Syndrome is a heart disorder characterized by abnormal electrocardiographic (ECG) findings and risk of sudden death. Patients should be advised to seek immediate emergency assistance if they experience fainting, light-headedness, abnormal heart beats, or shortness of breath because they may have a potentially life-threatening heart disorder known as Brugada Syndrome.

4.5 Interaction with other medicinal products and other forms of interaction
Caution should be used when lithium and diuretics are used concomitantly because diuretic-induced sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary.
Lithium levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg b.i.d. with celecoxib 200 mg b.i.d. as compared to subjects receiving lithium alone.
Concomitant use of lithium with a Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during SGLT2 inhibitor initiation and dosage changes.
Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

There is evidence that angiotensin-converting enzyme inhibitors, such as enalapril and captopril, and angiotension II receptor antagonists, such as losartan, may substantially increase steady-state plasma lithium levels, sometimes resulting in lithium toxicity. When such combinations are used, lithium dosage may need to be decreased, and plasma lithium levels should be measured more often.
Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea, and/or tinnitus. Caution is recommended. Concomitant administration of lithium with serotonergic drugs can precipitate serotonin syndrome. Monitor patients for signs and symptoms of serotonin syndrome, particularly during lithium initiation. If serotonin syndrome occurs, consider discontinuation of lithium and/or concomitant serotonergic drugs. Examples of serotonergic drugs include selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), and monoamine oxidase inhibitors (MAOI).
The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations, and alkalinizing agents such as sodium bicarbonate.
Concomitant administration of methyldopa, phenytoin, or carbamazepine with lithium may increase the risk of toxic effects of these drugs.
Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Adverse effects on implantation in rats, embryo viability in mice and metabolism *in vitro* of rat testes and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palates in mice.
In humans, lithium carbonate may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Breast-feeding

Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the infant or neonate. Signs and symptoms of lithium toxicity such as hypertonia, hypothermia, cyanosis, and ECG changes have been reported in some infants and neonates.

4.7 Effects on ability to drive and use machines

Lithium may cause disturbances of the CNS. Since lithium may slow reaction time, and considering the adverse reactions profile of lithium, patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable effects

Side effects are usually related to serum lithium concentration and are less common in patients with plasma lithium concentrations below 1.0 mmol/l. The adverse reactions usually subside with a temporary reduction or discontinuation of lithium treatment. Mild gastrointestinal effects such as nausea, a general discomfort and vertigo, may occur initially, but frequently disappear after the first few days of lithium administration. Fine hand tremors, polyuria and mild thirst may persist.

Tabulated list of adverse reactions

System Organ Class	**Adverse reactions**
Blood and lymphatic system disorders	Leucocytosis.
Endocrine disorders	• Long-term adverse effects may include thyroid function disturbances such as euthyroid goitre and/or hypothyroidism and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine. • Hypercalcaemia, hypermagnesaemia, hyperparathyroidism have been reported.
Metabolism and nutrition disorders	Weight increase, hyperglycaemia.
Psychiatric disorders	Confusion, delirium.
Nervous system disorders	• Ataxia, hyperactive deep tendon reflexes, slurred speech, dizziness, stupor, coma, myasthenia gravis, giddiness, dazed feeling, and memory impairment. • Tremor, especially fine hand tremors, dysarthria, myoclonus, benign intracranial hypertension. • Vertigo, impaired consciousness, abnormal reflexes, convulsions, extrapyramidal disorders, encephalopathy, cerebellar syndrome (usually reversible), nystagmus. The above symptoms may result in fall. • Peripheral neuropathy may occur on long-term treatment and is usually reversible at cessation of lithium. • Dysgeusia. • Serotonin syndrome • Neuroleptic malignant syndrome
Eye disorders	Blurred vision, scotoma.
Cardiac disorders	Cardiac arrhythmia, mainly bradycardia, sinus node dysfunction, peripheral circulatory collapse, hypotension, ECG changes such as reversible flattening or inversion of T-waves and QT prolongation, AV block, cardiomyopathy.
Gastrointestinal disorders	Abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, gastritis, salivary hypersecretion, dry mouth, anorexia.
Skin and subcutaneous tissue disorders	Folliculitis, pruritus, papular skin disorders, acne or acneform eruptions, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers. Frequency unknown: lichenoid drug reaction.
Musculoskeletal and connective tissue disorders	Muscle weakness, rhabdomyolysis
Renal and urinary disorders	• Polydipsia and/or polyuria and nephrogenic diabetes insipidus, histological renal changes with interstitial fibrosis after long term treatment have been reported. This is usually reversible on lithium

	withdrawal. • Long-term treatment with lithium may 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. • Rare cases of nephrotic syndrome have been reported. • Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy).
Reproductive system and breast disorders	Sexual dysfunction.
General disorders and administration site conditions	• Peripheral oedema. • Urticaria and angioedema, attributed to some excipients such as acacia powder (or Arabic gum).

If any of the above symptoms appear, treatment should be stopped immediately and arrangements made for serum lithium measurement.

4.9 Overdose

The toxic levels for lithium (≥ 1.5 mEq/L) are close to the therapeutic levels (0.6 to 1.2 mEq/L). It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. Toxic symptoms are listed in detail under adverse reactions section.

Treatment: No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance, and 3) regulation of kidney function. Urea, mannitol and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient.

Infection prophylaxis, regular chest X-rays and preservation of adequate respiration are essential.

5. Pharmaceutical properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Lithium, ATC code: N05AN01

Mood-stabilising agent

Lithium is an alkali metal available for medical use as lithium carbonate or lithium citrate. The exact mechanism of action of lithium in the treatment of bipolar disorders is not known.

The mode of action of lithium is still not fully understood. However, lithium modifies the production and turnover of certain neurotransmitters, particularly serotonin, and it may also block dopamine receptors.

It modifies concentrations of some electrolytes, particularly calcium and magnesium, and it may reduce thyroid activity.

5.2 Pharmacokinetic properties
Time to peak serum level for prolonged release Lithium carbonate tablets is about 2 hours and approximately 90% bioavailability would be expected.
Absorption
Lithium is rapidly absorbed from the gastrointestinal tract.
Steady-state lithium levels may not be obtained until 4-6 days.
Distribution
Lithium has a low volume of distribution (0.7 to 0.9 L/kg).
It is not bound to plasma proteins.
Lithium crosses the placenta and is excreted in breast milk.
Biotransformation
Lithium is not metabolised in the liver.
Elimination
Lithium is primarily excreted by the kidneys (>95% of the dose).
Elimination half-life ranges from 18 to 36 hours.
Lithium can be eliminated by haemodialysis.
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.

5.3 Preclinical safety data
Nothing of therapeutic relevance.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium Alginate NF
Sodium Starch Glycolate NF
Povidone USP
Ferric Oxide NF
Magnesium stearate NF
Purified Water USP

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30ºC. Protect from light and moisture.

6.5 Nature and content of container
Bottle pack of 100 tablets. Such 1 bottle is packed along with leaflet.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing authorization holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Division of J.B. Chemicals & Pharmaceuticals Ltd.)
Neelam center, B Wing, 4th floor, Hind cycle road,
Worli, Mumbai 400 030, INDIA

8. Marketing Authorization Number
06947/08096/NMR/2020

9. Date of First Authorization/Renewal of the Authorization
15/12/2021

10. Date of revision of the text
27/07/2023