Summary of Product Characteristics

1. Name of the medicinal product
Lithium Carbonate Extended-Release Tablets USP 300 mg

2. Qualitative and quantitative composition
Each Extended-Release Film Coated Tablet Contains:
Lithium Carbonate USP…….300 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 is indicated in the treatment of manic episodes of Bipolar Disorder. Bipolar Disorder, Manic (DSM-IV) is equivalent to Manic Depressive illness, Manic, in the older DSM-II terminology. Lithium carbonate is also indicated as a maintenance treatment for individuals with a diagnosis of Bipolar Disorder. Maintenance therapy reduces the frequency of manic episodes and diminishes the intensity of those episodes which may occur. 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 may produce a normalization of symptomatology within 1 to 3 weeks.

4.2 Posology and method of administration
Acute Mania
Optimal patient response can usually be established with 1800 mg/day in the following dosages:

ACUTE MANIA			
	Morning	**Afternoon**	**Night time**
Lithium Carbonate Extended-Release Tablet*	3 tabs (900 mg)		3 tabs (900 mg)

*Can also be administered on 600 mg TID recommended dosing interval.
Such doses will normally produce an effective serum lithium concentration ranging between 1 and 1.5 mEq/L. Dosage must be individualized according to serum concentrations and clinical response. Regular monitoring of the patient's clinical state and of serum lithium concentrations is necessary. Serum concentrations should be determined twice per week during the acute phase, and until the serum concentrations and clinical condition of the patient have been stabilized.
Long-Term Control
Desirable serum lithium concentrations are 0.6 to 1.2 mEq/L which can usually be achieved with 900 to 1200 mg/day. Dosage will vary from one individual to another, but generally the following dosages will maintain this concentration:

LONG- TERM CONTROL			
	Morning	**Afternoon**	**Night time**
Lithium Carbonate Extended-Release Tablet*	2 tabs (600 mg)		2 tabs (600 mg)

*Can be administered on TID recommended dosing interval up to 1200 mg/day.
Serum lithium concentrations in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months. Patients abnormally sensitive to

lithium may exhibit toxic signs at serum concentrations of 1 to 1.5 mEq/L. Geriatric patients often respond to reduced dosage, and may exhibit signs of toxicity at serum concentrations ordinarily tolerated by other 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 drug therapy.

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 previous dose). Total reliance must not be placed on serum concentrations alone. Accurate patient evaluation requires both clinical and laboratory analysis.
- 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 transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg pediatric patient who ingested 300 mg of lithium carbonate.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients.
• Severely impaired renal function.
• Untreated or untreatable hypothyroidism.
• Cardiac disease associated with rhythm disorder.
• Brugada syndrome or family history of Brugada syndrome (see section 4.4)
• Low body sodium levels for example dehydrated patients, those on low sodium diets, or those with Addison's disease.
• Breast-feeding.

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 patientnever exposed to lithium. The relationship between renal function 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 re-evaluation 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, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment 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

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 elimination half-life 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 (2500 to 3500 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 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 and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretic-, ACE-, and ARB-induced sodium loss may increase serum lithium concentrations. Start with lower doses of lithium or reduce dosage, while frequently monitoring serum lithium concentrations and signs of lithium toxicity. 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).

Concomitant administration of methyldopa, phenytoin, or carbamazepine with lithium may increase the risk of adverse reactions with these drugs.

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 extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism.

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.

Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

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 BID with celecoxib 200 mg BID as compared to subjects receiving lithium alone.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

4.6 Fertility, pregnancy and breastfeeding

Adverse effects on nidation in rats, embryo viability in mice, and metabolism in vitro of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium 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 by their physician 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 hazard 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.
Because of the potential for serious adverse reactions in nursing infants and neonates from lithium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
Lithium Carbonate Essential Pharma has minor to moderate influence on the ability to drive and use machines. As lithium may cause disturbances of the CNS, 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 concentrations and are less common in patients with plasma lithium concentrations below 1.0 mmol/l.
Initial Therapy: fine tremor of the hands, polyuria and thirst may occur.
Blood and lymphatic system disorders: leucocytosis. Immune system disorders: increase in antinuclear antibodies.
Endocrine disorders: disturbances of thyroid function including (euthyroid) goitre, hypothyroidism and hyperthyroidism, hyperparathyroidism, parathyroid adenoma.
Metabolism and nutrition disorders: hypercalcaemia, hypermagnesaemia, hyperglycaemia, anorexia, weight gain.
Psychiatric disorders: Delirium
Nervous system disorders: coma, benign intracranial hypertension, syndrome of irreversible lithium effectuated neurotoxicity (SILENT), encephalopathy, stupor, seizures, neuroleptic malignant syndrome, myasthenia gravis, serotonin syndrome, parkinsonism, extrapyramidal symptoms, ataxia, dizziness, memory impairment, mild cognitive impairment may occur during long term use, giddiness, nystagmus, slurred speech, vertigo, hyperactive deep tendon reflexes, dazed feeling, fine hand tremors.
Eye Disorders: scotomata and blurred vision.
Cardiac disorders: cardiac arrest, ventricular fibrillation, ventricular tachycardia, ventricular arrhythmias, Torsade de pointes, QT interval prolongation, cardiomyopathy, arrhythmia, bradycardia, sinus node dysfunction, ECG changes.
Vascular disorders: peripheral circulatory collapse, hypotension.
Gastrointestinal disorders: gastritis, nausea, diarrhoea, vomiting, dry mouth, excessive salivation. Lithium salts have been implicated in dysgeusia.
Skin and subcutaneous tissue disorders: Allergic rash, exacerbation of psoriasis, acneiform eruptions, alopecia, acne, papular skin disorder, folliculitis, pruritus, rash.
Frequency not known: lichenoid drug reaction
Musculoskeletal and connective tissue disorders: muscle weakness, rhabdomyolysis.
Renal and urinary disorders: symptoms of nephrogenic diabetes insipidus, impairment of renal function, permanent changes in the kidney, nephrotic syndrome, histological renal changes with interstitial fibrosis after long term treatment, polyuria, polydipsia.

Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy) (see section 4.4).
Reproductive system and breast disorders: sexual dysfunction
General disorders and administration site conditions: sudden unexplained death, oedema, asthenia, lethargy, thirst, fatigue, and malaise can occur due to lithium toxicity.
Some adverse events will be seen when Lithium levels are raised – for symptoms see section 4.9 Overdose.

4.9 Overdose
The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic concentrations. 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.
Treatment
No specific antidote for lithium poisoning is known. Treatment is supportive. 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 functioning. 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. However, patient recovery may be slow.
Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.

5. Pharmaceutical properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC-code: N05AN01
Mechanism of action
The precise mechanism of action of lithium as a mood-stabilising agent remains unknown, although many cellular actions of lithium have been characterised.

5.2 Pharmacokinetic properties
Distribution
It crosses the placenta and is excreted in breast milk.
The pharmacokinetics of lithium are extremely well documented. A single oral dose of lithium carbonate 250 gives a peak plasma level approximately 2-3 hours later, with the level at 24 hours being approximately 40% of peak levels.
Elimination
Lithium is excreted almost exclusively in the urine by the kidneys.
The half-life of lithium varies considerably between formulations, but generally is considered to be about 12 to 24 hours following a single dose.

Special populations
Elderly
Half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not be attained until 4 to 7 days after starting treatment.

5.3 Preclinical safety data
Lithium is teratogenic in rats and mice. In rats, lithium caused a reduction in fetal weights, numbers of live fetuses, delayed development of the skeleton and kidney toxicity in newborns at maternally toxic doses. In male rats, lithium caused morphological and histological changes in sperm tube epithelium and spermatids at doses comparable to human dosing, and reduced testicular weights and sperm production at doses more than 20 times higher than the human administered dose. The safety margin for these effects cannot be estimated due to an absence of exposure data.

6. Pharmaceutical particulars

6.1 List of excipients
H.P.M.C-Methocel K100LV CR Premium NF
Primojel Sodium Starch Glycoate NF
Povidone/Plasdone k-29/32 USP
Sodium Lauryl Sulfate NF
Calcium Stearate NF
Opadry Pink 03C540005
Purified Water BP

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 and 500 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
0649/07984/NMR/2019

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

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