

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

LITHOSUN SR 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated extended release tablet contains

Lithium carbonate USP..... 400 mg
Excipients.....q.s

For the full list of excipients, **see section 6.1.**

3. PHARMACEUTICAL FORM

Extended-release tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications¹

LITHOSUN SR 400 is indicated for treatment and prophylaxis of:

- Mania
- Bipolar disorder
- Recurrent depression
- Aggressive or self-harming behaviour

4.2 Posology and method of administration¹

LITHOSUN SR 400 is available in the strength of 400 mg only and may not be suitable for all the dosing recommendations mentioned below. In such cases, other approved strengths of lithium carbonate must be used.

Adult (body-weight up to 50 kg):

Initially 200–400 mg daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilized.

Adult (body-weight 50 kg and above):

Initially 0.4–1.2 g once daily, alternatively initially 0.4–1.2 g daily in 2 divided doses, dose adjusted according to serum lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilized.

Elderly:

Initially 200–400 mg daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilized.

Method of administration

Oral

4.3 Contraindications ²

- Hypersensitivity to lithium carbonate or to any of the excipients listed in section 6.1.
- 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 special precautions for use ²

General

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

The minimum clinically effective dose of lithium should always be used. Clear instructions regarding the symptoms of impending toxicity should be given by the physician to patients receiving long-term lithium therapy (see **section 4.8**). They should be warned of the urgency of immediate action should these symptoms appear, and also of the need to maintain a constant and adequate salt and water intake. At the first sign of toxicity, the patient should consult a physician and lithium levels should be checked. Treatment should be discontinued immediately on the first signs of toxicity (see **section 4.8**).

Monitoring recommendations

Before starting treatment with lithium, renal function, cardiac function and thyroid function should be evaluated. Patients should be euthyroid before initiation of lithium therapy. Lithium therapy is contraindicated in patients with severe renal insufficiency or cardiac insufficiency (see **section 4.3**).

Renal, cardiac and thyroid functions should be re-assessed regularly during treatment with lithium.

Renal impairment

Since lithium is primarily excreted via the renal route, significant accumulation of lithium may occur in patients with renal insufficiency. Therefore, if patients with mild or moderate renal impairment are being treated with lithium, serum lithium levels should be closely monitored and the dose should be adjusted accordingly. If very regular and close monitoring of serum lithium levels and plasma creatinine levels is not possible, lithium should not be prescribed in this population. Lithium is contraindicated in patients with severe renal insufficiency (see **section 4.3**).

The possibility of hypothyroidism and renal dysfunction arising during prolonged treatment should be borne in mind and periodic assessments made.

Patients should be warned to report if polyuria or polydipsia develop. In patients who develop polyuria and/or polydipsia (see **section 4.7**), renal function should be monitored in addition to the routine serum lithium assessment.

Renal tumours: Cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years (see **section 4.7**).

Fluid/electrolyte balance

If episodes of nausea, vomiting, diarrhoea, excessive sweating, and/or other conditions leading to salt/water depletion (including severe dieting) occur, lithium dosage should be closely monitored and dosage adjustments made as necessary. Drugs likely to upset electrolyte balance such as diuretics should also be reported. Indeed, sodium depletion increases the lithium plasma concentration (due to competitive reabsorption at the renal level). In these cases, lithium dosage should be closely monitored and reduction of dosage may be necessary.

Caution should be exercised to ensure that diet and fluid intake are normal in order to maintain 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 discontinuation should be considered during any intercurrent infection.

Risk of convulsions

The risk of convulsions may be increased in case of co-administration of lithium with drugs that lower the epileptic threshold, or in epileptic patients (see **sections 4.5** and **4.7**).

Benign intracranial hypertension

There have been case reports of benign intracranial hypertension (see **section 4.7**). Patients should be warned to report persistent headache and/or visual disturbances.

QT prolongation

As a precautionary measure, lithium should be avoided in patients with congenital long QT syndrome, and caution should be exercised in patients with risk factors such as QT interval prolongation (e.g. uncorrected hypokalaemia, bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QT interval (see **sections 4.5** and **4.7**).

Brugada syndrome

Lithium may unmask or aggravate Brugada syndrome, a hereditary disease of the cardiac sodium channel with characteristic electrocardiographic changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Lithium should not be administered to patients with Brugada Syndrome or a family history of Brugada Syndrome (see **section 4.3**). Caution is advised in patients with a family history of cardiac arrest or sudden death.

Bariatric surgery

A lower maintenance dosage of lithium may be required for patients, who have undergone a bariatric surgery because of decreased glomerular filtration following marked weight loss. Also, drug levels should be monitored closely in connection with bariatric surgery due to the risk of lithium toxicity.

Elderly patients

Elderly patients are particularly liable to lithium toxicity and may exhibit adverse reactions at serum levels ordinarily tolerated by younger patients. Caution is also advised since lithium excretion may be reduced in the elderly due to age related disease in renal function (see **section 5.2**).

Paediatric population

The use in children is not recommended.

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 (see **section 4.7**), patients should be warned of the possible hazards when driving or operating machinery.

Excipients

This medicine contains less than 1 mmol sodium (0.150 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other finished pharmaceutical products (fpps) and other forms of interaction ^{1, 2}

Interactions which increase lithium concentrations

Serum lithium levels may be increased if one of the following drugs is coadministered. When appropriate, either lithium dosage should be adjusted or concomitant treatment stopped.

- Metronidazole may reduce lithium renal clearance.
- Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase (COX) 2 inhibitors (monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Angiotensin II receptor antagonists.
- Diuretics (thiazides show a paradoxical antidiuretics effect resulting in possible water retention and lithium intoxication). If a thiazide diuretic has to be prescribed for a lithium-treated patient, lithium dosage should first be reduced and the patient re-stabilised with frequent monitoring. Similar precautions should be exercised on diuretic withdrawal. Loop diuretics seem less likely to increase lithium levels.
- Other drugs affecting electrolyte balance, e.g. steroids, may alter lithium excretion and should therefore be avoided.
- Tetracyclines.
- Aldosterone antagonists (eplerenone, spironolactone)

Interactions which decrease serum lithium concentrations

Serum lithium levels may be decreased due to an increase in lithium renal clearance in case of concomitant administration of one of the following drugs:

- Xanthines (theophylline, caffeine).
- Sodium bicarbonate containing products.
- Diuretics (osmotic and carbonic anhydrase inhibitors).
- Urea
- Calcitonin
- Empagliflozin
- Aminophylline

Interactions causing neurotoxicity

Co-administration of the following drugs may increase the risk of neurotoxicity:

- Antipsychotics (particularly haloperidol at higher dosages), flupentixol, diazepam, thioridazine, fluphenazine, chlorpromazine and clozapine may lead in rare cases to severe neurotoxicity with symptoms such as confusion, disorientation, lethargy, tremor, extra-pyramidal symptoms and myoclonus. Increased lithium levels were present in some of the reported cases. Co-administration of antipsychotics and lithium may increase the risk of Neuroleptic Malignant Syndrome, which may be fatal. Discontinuation of both drugs is recommended at the first signs of neurotoxicity.
- Methyldopa.
- Triptan derivatives and/or serotonergic antidepressants such as Selective Serotonin Re-uptake Inhibitors (e.g. fluvoxamine and fluoxetine) as this combination may precipitate a serotonergic syndrome*, which justifies immediate discontinuation of treatment.
- Calcium channel blockers may lead to neurotoxicity with symptoms such as ataxia, confusion and somnolence. Lithium concentrations may be increased.
- Carbamazepine may lead to dizziness, somnolence, confusion and cerebellar symptoms such as ataxia.
- Oxcarbamazepine
- Quetiapine
- Risperidone
- Zuclopenthixol

Other

Caution is advised if lithium is co-administered with other drugs that prolong the QT interval (see **sections 4.4** and **4.7**), e.g. Class IA (e.g. quinidine, disopyramide), or Class III (e.g. amiodarone) antiarrhythmic agents, cisapride, antibiotics such as erythromycin, antipsychotics such as thioridazine or amisulpride. The list is not comprehensive.

Caution is advised if lithium is co-administered with drugs that lower the epileptic threshold (see **section 4.4**), e.g. antidepressants such as SSRIs, tricyclic antidepressants, antipsychotics, anaesthetics, theophylline. The list is not comprehensive.

Lithium may prolong the effects of neuromuscular blocking agents. There have been reports of interaction between lithium and phenytoin, indomethacin and other prostaglandin-synthetase inhibitors.

**Serotonin syndrome*

Serotonin syndrome is a potentially life-threatening adverse reaction, which is caused by an excess of serotonin (e.g. from overdose or concomitant use of serotonergic drugs), necessitating hospitalisation and even causing death.

Symptoms may include:

- Mental status changes (agitation, confusion, hypomania, eventually coma)
- Neuromuscular abnormalities (myoclonus, tremor, hyperreflexia, rigidity, akathisia)
- Autonomic hyperactivity (hypo or hypertonia, tachycardia, shivering, hyperthermia, diaphoresis)
- Gastrointestinal symptoms (diarrhoea)

Strict adherence to the recommended doses is an essential factor for the prevention of the occurrence of this syndrome.

Acetazolamide alters the concentration of lithium. Potassium-sparing diuretics (triamterene) potentially increase the clearance of lithium.

4.6 Use in Pregnancy and lactation ²

Pregnancy

Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. There is epidemiological evidence that it may be harmful to the foetus in human pregnancy. Lithium crosses the placental barrier. Lithium has been reported to interfere with fertility, gestation and foetal development in animals. Cardiac especially Ebstein anomaly, and other malformations have been reported. Therefore, 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 treatment during pregnancy, serum lithium levels should be closely monitored and measured frequently since renal function changes gradually during

pregnancy and suddenly at parturition. Dosage adjustments are required. It is recommended that lithium be discontinued shortly before delivery and reinitiated a few days post-partum.

Neonates may show signs of lithium toxicity including symptoms such as lethargy, flaccid muscle tone, or hypotonia. Careful clinical observation of the neonate exposed to lithium during pregnancy is recommended and lithium levels may need to be monitored as necessary.

Women of child-bearing potential

Women of child-bearing potential should use effective contraceptive methods during treatment with lithium.

Breast-feeding

Lithium is secreted in breast milk and there have been case reports of neonates showing signs of lithium toxicity. Therefore lithium should not be used during breastfeeding (see **section 4.3**). A decision should be made whether to discontinue lithium therapy or to discontinue breast-feeding, taking into account the importance of the drug to the mother and the importance of breast-feeding to the infant.

Fertility

Spermatogenesis abnormalities that may lead to impairment of fertility have been reported in rats exposed to lithium. This risk may also potentially apply to humans.

4.7 Undesirable effects ²

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, memory impairment. - Tremor, especially fine hand tremors, dysarthria, myoclonus, benign intracranial hypertension (see section 4.4), - Vertigo, impaired consciousness, abnormal reflexes, convulsions (see sections 4.4 and 4.5), 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 (see sections 4.4 and 4.5), 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 acneiform 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 (see section 4.4). 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) (see section 4.4).
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

<https://pv.pharmacyboardkenya.org>

4.8 Overdose ²

In patients with a raised lithium concentration, the risk of toxicity is greater in those with the following underlying medical conditions: hypertension, diabetes, congestive heart failure, chronic renal failure, schizophrenia, Addison's disease.

Acute

A single acute overdose usually carries low risk and patients tend to show mild symptoms only, irrespective of their serum lithium concentration. However more severe symptoms may occur after a delay if lithium elimination is reduced because of renal impairment, particularly if a slow-release preparation has been taken. The fatal dose, in a single overdose, is probably over 5 g.

If an acute overdose has been taken by a patient on chronic lithium therapy, this can lead to serious toxicity occurring even after a modest overdose as the extravascular tissues are already saturated with lithium.

Chronic

Lithium toxicity can also occur in chronic accumulation for the following reasons: Acute or chronic overdosage; dehydration e.g. due to intercurrent illness, deteriorating renal function, drug interactions, most commonly involving a thiazide diuretic or a non-steroidal anti-inflammatory drug (NSAID).

Symptoms

The onset of symptoms may be delayed, with peak effects not occurring for as long as 24 hours, especially in patients who are not receiving chronic lithium therapy or following the use of a sustained release preparation.

Symptoms of lithium intoxication include:

Mild: Nausea, diarrhoea, blurred vision, polyuria, light headedness, fine resting tremor, muscular weakness and drowsiness.

Moderate: Increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, choreoathetoid movements, urinary or faecal incontinence, increasing restlessness followed by stupor. Hypernatraemia.

Severe: Coma, convulsions, cerebellar signs, cardiac dysrhythmias including sinoatrial block, sinus and junctional bradycardia and first degree heart block. Hypotension or rarely hypertension, circulatory collapse and renal failure.

Others:

Gastrointestinal disorders: increasing anorexia and vomiting.

Nervous system disorders: Encephalopathy, cerebellar syndrome with symptoms such as muscle weakness, lack of coordination, drowsiness or lethargy, giddiness, ataxia, nystagmus, coarse tremor. Tinnitus, dysarthria, twitching, myoclonus, extrapyramidal disorders.

ECG changes (flat or inverted T waves, QT prolongation), AV block, dehydration and electrolyte disturbances.

At blood levels above 2-3 mmol/l, there may be a large output of dilute urine and renal insufficiency, with increasing confusion, convulsions, coma and death.

Management

There is no specific antidote to lithium. In the event of lithium overdose, lithium should be discontinued and lithium serum levels monitored closely.

Supportive treatment should be initiated, which includes correction of fluid and electrolyte balance, if necessary.

Diuretics should not be used (see **section 4.5**). All patients should be observed for a minimum of 24 hours. ECG should be monitored in symptomatic patients. Steps should be taken to correct hypotension.

Consider gastric lavage for non-sustained-release preparations if more than 4 g has been ingested by an adult within 1 hour or definite ingestion of a significant amount by a child. Slow-release tablets do not disintegrate in the stomach and most are too large to pass up a lavage tube. Gut decontamination is not useful for chronic accumulation. Activated charcoal does not adsorb lithium.

Haemodialysis is the treatment of choice for severe lithium intoxication (especially in patients manifesting with severe nervous system disorders), or in cases of overdose accompanied by renal impairment.

Haemodialysis should be continued until there is no lithium in the serum or dialysis fluid. Serum lithium levels should be monitored for at least another week to take account of any possible rebound in serum lithium levels as a result of delayed diffusion from the body tissues.

In cases of acute on chronic overdose or in cases of chronic lithium toxicity if the lithium concentration is >4.0 mmol/l, discuss with your local poisons service.

Clinical improvement generally takes longer than reduction of serum lithium concentrations regardless of the method used.

5. PHARMACOLOGICAL PROPERTIES²

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 Pharmacokinetics properties

Time to peak serum level for prolonged release lithium carbonate tablets is reported to be 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 reported to be primarily excreted by the kidneys (>95% of the dose). Elimination half-life has been reported to range 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 (see **section 4.4**).

5.3 Preclinical safety data²

Nothing of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose IP / Lactose Monohydrate NF, Starch (Maize) IP / Maize Starch BP, Dibasic Calcium Phosphate IP (Dihydrate) / Calcium Hydrogen Phosphate BP, Microcrystalline Cellulose, Hydroxy propyl Methyl Cellulose IP/ Hypromellose K4M USP, Hydroxy propyl Methyl Cellulose IP / Hypromellose USP (K15M Premium,2208), Sodium Methyl Hydroxy Benzoate IP/BP, Hydroxy propyl Methyl Cellulose IP / Hypromellose 2910 USP (E-5 Premium), Isopropyl Alcohol BP, Purified Water, Talc IP/ Purified Talc BP, Magnesium Stearate IP/BP.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 Months

6.4 Special precautions for storage

Store up to 30°C, protect from light.

6.5 Nature and contents of container

A flat beveled edge, white, circular uncoated tablet, having mark of “LITHOSUN SR” on one side & plain on the other side.
10 tablets are packed in strip, just 3 strips are packed in carton along with package insert.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited.
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Mumbai – 400 063, India.

Manufacturing site:

Sun Pharma Laboratories Limited (SPLL) 6-9, EPIP Kartholi, Bari
Brahmana, Jammu-181133 (J&K) India.

8. MARKETING AUTHORISATION NUMBER(S)

H95/527

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

April 2022

10. DATE OF REVISION OF THE TEXT

April 2022