PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**LITHMAX®**

Lithium Carbonate

Sustained-Release Tablets

300 mg

Oral

House Standard

Anti-Manic Agent

AA PHARMA INC
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7
www.aapharma.ca

Date of Initial Authorization:
MAR 31, 2005

Date of Revision:
APR 01, 2025

Submission Control Number: 291317

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	04/2025
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	04/2025
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	04/2025
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment,Table 1: Lithium Dosing	04/2025
4 DOSAGE AND ADMINISTRATION, 4.5 Missed Dose	04/2025
7 WARNINGS AND PRECAUTIONS, Cardiovascular	04/2025
7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance	04/2025
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests	04/2025
7 WARNINGS AND PRECAUTIONS, Neurologic	04/2025
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	04/2025
7 WARNINGS AND PRECAUTIONS, Skin	04/2025

TABLE OF CONTENTS

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LITHMAX (lithium carbonate sustained-release tablets) is indicated for:

- the lithium treatment of manic episodes of manic-depressive illness.

Maintenance therapy has been found useful in preventing or diminishing the frequency of subsequent relapses in bipolar manic-depressive patients (with a history of mania).

1.1 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LITHMAX in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from post-market experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 8.1 Adverse Reaction Overview and 4.2 Recommended Dose and Dosage Adjustment, Geriatrics.

2 CONTRAINDICATIONS

LITHMAX (lithium carbonate sustained-release tablets) is contraindicated in:

- patients with significant brain damage,
- renal or cardiovascular disease,
- severe debilitation or dehydration,
- sodium depletion,
- patients receiving diuretics;

For the above contraindications in such patients, the risk of lithium toxicity is very high.

For these patients with a high risk of lithium toxicity, if the psychiatric indication is life-threatening and if such a patient fails to respond to other measures, lithium treatment may be undertaken, in selected cases, with extreme caution. This includes a thorough medical assessment and appropriate consultation for at-risk patients, daily serum lithium determinations and adjustments of the doses to levels tolerated by the individual patient. In such instances, hospitalization is a necessity.

LITHMAX (lithium carbonate sustained-release tablets) is also contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Lithium toxicity

- Lithium toxicity is closely related to serum lithium levels and can occur at doses close to the therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy. See 4.1. Dosing Considerations, 4.2. Recommended Dose and Dosage Adjustment and 7. WARNINGS AND PRECAUTIONS, General.
- Outpatients and their families should be warned that the patient must discontinue therapy with lithium carbonate sustained-release tablets and contact the healthcare professional if clinical signs of lithium toxicity such as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur. See 7. WARNINGS AND PRECAUTIONS, Renal
- There is evidence of decreased tolerance to lithium once the acute manic episode breaks. Therefore, when the acute attack subsides, the dosage should be reduced rapidly in order to produce serum lithium levels no higher than between 0.6 and 1.2 mmol/L. 4.1 Dosing Considerations, 4.2 Recommended Dose and Dosage Adjustment and 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Before initiating treatment with lithium, renal function, vital signs, serum electrolytes, and thyroid function should be evaluated. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and 7 WARNINGS AND PRECAUTIONS, Renal. Concurrent medications should be assessed, and if the patient is a woman of childbearing potential, pregnancy status and potential should be considered. See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations.

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to the therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside. See 4.2 Recommended Dose and Dosage Adjustment, Acute Mania.

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 1.0 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.

Typical symptoms of mania, as an affective disorder, include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity or 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.

Selection of Patients and Approach to Lithium Therapy

Screening for lithium candidates should include at least a medical history and physical examination with emphasis on the urinary, cardiovascular, gastrointestinal, endocrine and central nervous systems, and the skin. It should also include routine 24-hour urine volume, serum creatinine, record of weight, an ECG, possibly electrolytes and TSH, and for long-term treatment, creatinine clearance and a urine concentration test. Other examinations and tests should be used when indicated. Monitoring lithium treatment should include, for each visit, mental status, physical examination, weight, 12-hour serum lithium and a check for lithium side effects and compliance. It should also include serum creatinine every 2 months, plasma thyroid hormone and TSH every 6 to 12 months (particularly in female patients) and attention to renal and thyroid function should be maintained throughout, with tests used for baseline screening repeated, as required. Also, consider serum calcium level before onset of treatment, after 6 months, and yearly thereafter in long-term treatment.

The first objective of treatment is to establish an effective and safe daily dosage of lithium, with the aid of standardized 12-hour serum lithium levels, maintained within the therapeutic range, as high as necessary for efficacy, and with the patient as much as possible free of significant side effects. Two daily doses should be used initially, at least until the daily dosage is established. The next aim is to move to an optimal dose, which should be as low as possible, consistent with protection against relapse. During follow-up, an adjustment to lower dosages may be required to minimize adverse effects, and a change in the lithium preparation used and/or the frequency of dosing, either towards multiple doses or towards a single dose, may be necessary to handle absorption-related adverse effects or concern over possible renal toxicity. Intermittent lithium treatment in carefully selected patients has been recommended by some lithium experts, but should not be undertaken without careful planning and great caution. The co-operation of patients and relatives is required throughout.

Maintaining a patient with a lithium non-responsive condition on long-term therapy poses an unacceptable risk. The following are among the factors to be re-assessed before a decision is made: careful reconfirmation of the diagnosis of primary affective disorder; the health status of the patient; the side effects of lithium therapy experienced by the patient; and the response to treatment.

4.2 Recommended Dose and Dosage Adjustment

Acute Mania

The therapeutic dose for the treatment of acute mania should be based primarily on the patient's clinical condition. It must be individualized for each patient according to blood levels and clinical response. Manic patients usually require serum lithium levels in excess of 1 mEq/L and the dosage should be adjusted to obtain serum levels between 1 and 1.5 mEq/L (in blood samples drawn before the patient has had his first lithium dose of the day).

In properly screened adult patients with good renal function, the suggested initial dosage for acute mania is 1200 to 1800 mg (approximately 50 mEq/L) divided into 2 doses and administered at 12-hour intervals. In view of the large variability of renal lithium excretion among individuals, it is suggested that lithium treatment be started at a dose between 600 and 900 mg/day, reaching a level of 1200 to 1800 mg/day, in 2 divided doses, on the second day.

Depending on the patient's clinical condition, the initial dosage should be adjusted to produce the desired serum lithium level. The weight of the patient should also influence the choice of the initial dose.

Geriatrics (≥65 years of age): Lithium should be used cautiously and in reduced doses in the geriatrics patient, usually in the range of 600 to 1200 mg/day or less, starting with smaller doses (see 7 WARNINGS AND PRECAUTIONS, Renal). Serum lithium levels must always be checked carefully and frequently during initiation of treatment, monitored regularly thereafter and should be kept below 1.5 mEq/L.

Maintenance Therapy

After the acute manic episode subsides, usually within a week, the dosage should be rapidly reduced to achieve serum levels between 0.6 and 1.2 mEq/L, since there is evidence of a decreased tolerance to lithium at this time. The average suggested dosage at this stage is 900 mg/day (approximately 25 mEq/L) administered in a single dose at bedtime, with a range usually between 600 and 1200 mg/day. If a satisfactory response is not obtained within 14 days, lithium therapy should be discontinued. When the manic attack is controlled, lithium administration should be maintained for the expected duration of the manic phase, since early withdrawal might lead to relapse. Long-term lithium treatment has been found useful for relapse prevention (see 4.1 Dosing Considerations, Selection of Patients and Approach to Lithium Therapy). It is essential to maintain clinical supervision of the patient and to monitor serum lithium levels as required during treatment (see 7 WARNINGS AND PRECAUTIONS). Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every 2 months.

Pediatrics (<12 years of age): Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Geriatrics (≥65 years of age): Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0 to 1.4 mEq/L. Geriatrics patients often respond to reduced dosage and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients.

N.B.: Blood samples for serum lithium determination should be drawn prior to the next dose and when lithium concentrations are relatively stable (i.e., 10 to 14 hours after the previous dose of lithium). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical assessment and laboratory analyses.

Table 1: Lithium Dosing

	Acute Mania		Long-Term Control (usually within a week of manic episode subsides)
	Treatment Initiation	**Day 2 and onward**	
Adults	600 to 900 mg/day in 2 divided doses	1200 to 1800 mg in divided doses (serum lithium concentration reaching 1 to 1.5 mmol/L)	600 to 1200 mg/day with a suggested dose of 900 mg/day in a single dose at bed time (serum lithium concentration of 0.6 to 1.2 mmol/L
Geriatric		600 to 1200 mg/day (serum lithium concentration below 1.5 mmol/L)	

4.4 Administration

LITHMAX should be swallowed whole or broken in half.

They should not be chewed or crushed.

4.5 Missed Dose

In case of missed dose, the next dose should be taken at your usual time. A double dose should not be taken.

5 OVERDOSAGE

The toxic levels for lithium are close to the therapeutic levels. It is therefore important that patients and their families be cautioned to watch for early symptoms of overdosage and to discontinue LITHMAX and inform the physician should they occur. Early signs of toxicity which may occur at serum lithium levels lower than 2 mEq/L were described under ADVERSE REACTIONS and usually respond to reduction of dosage. Lithium intoxication has been preceded by the appearance or aggravation of the following symptoms: sluggishness, drowsiness, lethargy, coarse tremors or muscle twitchings, loss of appetite, vomiting and diarrhea. Occurrence of these symptoms requires immediate cessation of medication and careful clinical re-assessment of management. Signs and symptoms of lithium intoxication have already been described under 8 ADVERSE REACTIONS.

Treatment

No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction in the dosage or cessation of the drug and resumption of 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 and supportive care.

Recommended treatment consists of: 1) correction of fluid and electrolyte imbalance and 2) 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-ray, and preservation of adequate respiration are essential.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Sustained release tablet, 300 mg of lithium carbonate	Hydroxypropyl methylcellulose and magnesium stearate.

LITHMAX (lithium carbonate sustained-release tablets): each round, white, flat-faced, beveled-edge tablet, scored and engraved “LIT” over “300” on one side and plain on the other, contains 300 mg of lithium carbonate. Available in bottles of 100. Lithium carbonate is a prescription drug.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Cardiovascular

Patients with underlying cardiovascular disease should be observed carefully for signs of arrhythmias.

Dependence/Tolerance

After the acute manic episode subsides, usually within a week, the dosage of LITHMAX should be rapidly reduced since there is evidence at this time of a decreased tolerance to lithium; see 4.2 Recommended Dose and Dosage Adjustment.

Driving and Operating Machinery

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

Endocrine and Metabolism

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium therapy; where hypothyroidism 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.

- **Parathyroid Abnormalities**

  A systematic review and meta-analysis indicates that about 10% of patients on long-term lithium therapy may develop hypercalcemia with or without hyperparathyroidism. Screening of serum calcium level and if necessary serum parathormone level need to be considered.

- **Parathyroid Disorders**

  Hypercalcemia with or without hyperparathyroidism has been reported in patients on lithium therapy. Screening of serum calcium level and if necessary serum parathormone level need to be considered.

Monitoring and Laboratory Tests

To maximize benefits, minimize the risks, and reduce as much as possible the adverse effects of lithium therapy, it is essential to provide proper information to patients and relatives about the treatment regimen and clinical exams required before and during treatment, as well as an explanation of the expected benefits and the most commonly experienced immediate and long-term side effects. Appropriate written material should be provided to supplement verbal information. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 4.1. Dosing Considerations.

Neurologic

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leucocytosis, elevated serum enzymes, blood urea nitrogen (BUN) and fasting blood sugar (FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear (see 9.4 Drug-Drug interactions, Haloperidol). The possibility of similar adverse interactions with other antipsychotic medication exists (see 9.4 Drug-Drug interactions).

Renal

- **Impaired Renal Function**

Chronic lithium therapy is frequently associated with a decrease in renal concentrating capacity with development of thirst, polyuria, nycturia, weight gain and altered kidney function tests, occasionally presenting as nephrogenic diabetes insipidus. Such patients should be managed carefully to avoid dehydration with resulting lithium retention and toxicity. The evidence suggests that impaired renal function during chronic therapy may be, in most instances, only partially reversible when lithium is discontinued.

Prevention of renal toxicity and other toxic effects of long-term therapy requires a firm diagnosis of bipolar manic-depressive illness; careful screening for pre-existing renal and other diseases; establishment of standardized 12-hour serum lithium levels which are as low as possible yet clinically effective; maintaining control of treatment by monitoring serum lithium levels and exercising clinical and laboratory surveillance over possible side effects or signs of lithium intoxication; exercising maximum control of at-risk patients; ensuring that long-term lithium therapy is maintained only when clinical response has been clearly established; and adjusting the dosage schedule and preparation used so as to obtain temporarily periods of lithium concentrations as low as possible in the kidney.

Glomerular sclerosis and interstitial fibrosis, as well as tubular lesions, have been reported in patients on chronic lithium therapy.

When kidney function is assessed for baseline data prior to starting lithium therapy or thereafter, routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality or 24-hour urine volume) and glomerular function (e.g. serum creatinine or creatinine clearance).

During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for re-evaluation of treatment, including dosage and frequency of lithium administration, and a re-assessment of the risk-benefit of long-term lithium therapy.

Lithium decreases sodium re-absorption by the renal tubules, which would 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 3000 mL), at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if these occur, supplemental fluid and salt should be administered. In addition to sweating and diarrhea, concomitant infection, with elevated temperatures, may also necessitate a temporary reduction or cessation of medication.

Reproductive Health: Female and Male Potential

- **Fertility**

  Lithium decreases the fertility of male rats and is spermicidal in vitro for human and animal spermatozoa (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Skin

Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) for which lithium carbonate was suspected to have contributed were reported.

7.1 Special Populations

7.1.1 Pregnant Women

Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly; nephrogenic diabetes insipidus, euthyroid goiter and hypoglycemia have occurred in infants born to women who took lithium during pregnancy. Therefore, lithium should not be used during pregnancy or in women of childbearing potential unless it cannot be substituted by other appropriate therapy and, in the opinion of the physician, the expected benefits outweigh the possible hazards to the fetus. See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology. Consider contraception for both females and males.

7.1.2 Breast-feeding

Lithium is excreted in human milk. Breast-feeding 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 child.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from post-market experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Mild side effects may be encountered even when serum lithium levels remain below 1 mEq/L. The most frequent side effects are the initial post-absorptive symptoms, believed to be associated with a rapid rise in serum lithium levels. They include nausea, abdominal pain, vomiting, diarrhea, vertigo, muscle weakness, sleepiness and a dazed feeling, and they frequently disappear after stabilization of therapy. The more common and persistent adverse reactions are fine tremor of the hands (which is not responsive to antiparkinson drugs) and, at times, fatigue, thirst and polyuria (renal toxicity). These side effects may subside with continued treatment, or a temporary reduction or cessation of dosage. If persistent, a lowering or cessation of dosage and reassessment of lithium therapy is indicated.

Mild to moderate toxic reactions may occur at lithium levels from 1.5 to 2 mEq/L, and moderate to severe reactions at levels above 2 mEq/L. Permanent neurological damage has been reported after exposure to toxic levels of lithium.

A number of patients may experience lithium accumulation during initial therapy, increasing to toxic levels and requiring immediate discontinuation of the drug. Some geriatrics patients with lowered renal clearances for lithium may also experience different degrees of lithium toxicity, requiring reduction or temporary withdrawal of medication. However, in patients with normal renal clearance the toxic manifestations appear to occur in a fairly regular sequence related to serum lithium levels. The usually transient Gl symptoms are the earliest side effects to occur. A mild degree of fine tremor of the hands may persist throughout therapy. Thirst and polyuria may be followed by increased drowsiness, ataxia, tinnitus and blurred vision, indicating early intoxication. As intoxication progresses the following manifestations may be encountered: confusion, increasing disorientation, muscle twitching, hyperreflexia, nystagmus, seizures, diarrhea, vomiting, and eventually coma and death.

8.5 Post-Market Adverse Reactions

The following toxic reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range.

Cardiac disorders: Cardiac arrhythmia.

Endocrine disorders:

Euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4 levels and elevated TSH. Iodine^{131} uptake may be elevated. On the average, 5 to 15% of patients on long-term lithium therapy manifest clinical signs or have altered serum hormone levels. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism. Paradoxically, rare cases of hyperthyroidism have been reported.

Eye disorders: Blurred Vision, visual field defect.

Gastrointestinal disorders: Nausea, vomiting, diarrhea, dry mouth.

General disorders and administration site conditions: Ataxia, fatigue, lethargy.

Investigations: Weight loss, electroencephalogram abnormal (Diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm). Electrocardiogram abnormal (Reversible flattening, isoelectricity or inversion of T waves).

Metabolism and nutrition disorders: Anorexia, dehydration.

Musculoskeletal and connective tissue disorders: Rippling muscle disease (muscle twitching, tonic clonic movements of whole limbs).

Central and Peripheral Nervous system disorders: Tremor, muscle hyperirritability (fasciculation, twitching, especially of facial muscles and clonic movements of the limbs), hypertonicity, ataxia, choreoathetotic movement, hyperactive deep tendon reflexes, extrapyramidal symptoms including acute dystonia and parkinsonism, general muscle weakness, urinary and fecal incontinence, slurred speech, blackout spells, seizures, cranial nerve involvement, psychomotor retardation, somnolence, dizziness, toxic confusional states, restlessness, stupor, coma, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes, myasthenic syndromes (rarely).

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.

EEG Changes: Diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm. Sensitivity to hyperventilation and paroxysmal bilateral synchronous delta activity have also been described.

Psychiatric disorder: Psychomotor retardation, confusional state.

Renal and urinary disorders: Albuminuria, oliguria, polyuria, glycosuria.

Skin and subcutaneous tissue disorders: Dry hair and hair thinning, anesthesia of skin, acne, chronic folliculitis, dry skin, alopecia and exacerbation of psoriasis, rash, pruritus, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Vascular disorders: Hypotension, peripheral circulatory failure.

Post-Market Miscellaneous Reactions Frequently Unrelated to Dosage

Blood and lymphatic system disorders: Leukocytosis.

Investigations: Transient electroencephalographic and electrocardiographic changes, excessive weight gain.

Metabolism and nutrition disorders: Diffuse non-toxic goiter with or without hypothyroidism, transient hyperglycemia.

Musculoskeletal and connective tissue disorders: Edematous swelling of ankles or wrists.

Nervous system disorders: Headache, worsening of organic brain syndrome, metallic taste.

Renal and urinary disorders: Albuminuria, thirst or polyuria sometimes resembling diabetes insipidus.

Skin and subcutaneous tissue disorders: Generalized pruritus with or without rash, cutaneous ulcers.

A single instance has been reported of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

Post-Market Serious Reactions to Long-term Therapy

In addition to other possible adverse reactions, the main concern during chronic lithium therapy centres on kidney function, the thyroid, parathyroid, the bones and the skin.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Bronchodilators, Aminophylline or Theophylline	CT	The administration of aminophylline or theophylline to patients on lithium therapy may require increased lithium doses to maintain the psychotropic effect. Theophylline enhances the renal clearance of lithium in most patients, thus tending to reduce serum lithium concentrations.	When initiating lithium therapy in a patient on chronic theophylline, lithium dosage requirements may be higher than anticipated. When initiating theophylline therapy in a patient on chronic lithium, there may be reduced lithium response. Discontinuation of theophylline in a patient on chronic lithium may result in excessive lithium response. Monitoring of serum lithium concentration is recommended.
Calcium Channel Blockers (CCBs)	T	The addition of verapamil or diltiazem to patients stabilized on lithium therapy may result in neurotoxicity. The CCB effects may be additive to that of lithium on transmitter secretion in the nervous system.	The use of CCBs in the treatment of patients with bipolar disorders receiving lithium should be commenced carefully with observation for neurotoxic effects. The therapeutic range of lithium may need to be toward the lower end when a CCB is coadministered.
Carbamazepine or Phenytoin	C	Concurrent use of lithium and carbamazepine or phenytoin might result in an increased risk of central nervous system toxicity.	Monitor patients closely for adverse reactions of phenytoin. Patients should be monitored for evidence of lithium toxicity when carbamazepine is given

Proper/Common name	Source of Evidence	Effect	Clinical comment
		Several cases of neurotoxicity (in the absence of toxic serum lithium concentrations) have been reported in patients receiving lithium and carbamazepine, but the combination has also been used to advantage in some manic patients.	concurrently. It is not yet established whether plasma lithium concentrations are useful in monitoring this interaction since the carbamazepine might increase the effect of lithium without increasing plasma lithium concentrations.
Diazepam	C	An isolated case has been reported of serious hypothermia during concurrent treatment with lithium and diazepam.	Since hypothermia is potentially fatal if it occurs and its general incidence is not known, it would be prudent to watch for this interaction during concurrent treatment.
Diuretics or Angiotensin Converting Enzyme (ACE) Inhibitors, including captopril	T	Caution should be exercised when lithium and diuretics or ACE inhibitors are used concomitantly because sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity.	When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium plasma levels is recommended (see also 7 WARNINGS AND PRECAUTIONS, Renal).
Haloperidol	T	It has been proposed that haloperidol and lithium could have a combined inhibitory effect on striatal adenylate cyclase. An encephalopathy resembling malignant neuroleptic syndrome (characterized by weakness; lethargy; fever; tremulousness and confusion; extrapyramidal symptoms; leukocytosis; and elevated serum	If haloperidol and lithium are used concomitantly, careful attention should be given to the dose of both agents as well as to early evidence of neurological toxicity, such as rigidity and/or hyperpyrexia, particularly in the presence of one or more predisposing factors which include large doses of one or both drugs, the presence of acute mania, failure to discontinue drugs when adverse effects occur, pre-existing brain damage, a

Proper/Common name	Source of Evidence	Effect	Clinical comment
		enzymes, BUN and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and concomitant administration of lithium and haloperidol has not been clearly established.	history of extrapyramidal symptoms with neuroleptic therapy alone, the concurrent use of anticholinergic antiparkinsonian drugs, and the presence of other physiologic disturbances such as infection, fever, or dehydration (see also 7 WARNINGS AND PRECAUTIONS, Neurologic).
Indomethacin and other Non-Steroidal Anti-Inflammatory Drugs (NSAID)s	C	Indomethacin has been reported to increase steady-state plasma lithium levels by 30 to 59%. There is also evidence that other non-steroidal anti-inflammatory agents may have a similar effect.	In a patient stabilized on lithium and NSAIDs, discontinuation of the NSAIDs may result in inadequate serum lithium concentrations. When such combinations are used, increased frequency of monitoring plasma lithium levels is recommended.
Mazindol	C	Isolated cases of lithium toxicity have been reported to be induced by concomitant administration of mazindol.	
Methyldopa or Tetracycline	C	There are reports that concurrent use of methyldopa or tetracycline may increase the risk of lithium toxicity.	Monitor patients closely for adverse reactions of methyldopa.
Neuromuscular blocking agents	T	The action of neuromuscular blocking agents (e.g., succinylcholine, pancuronium)may be prolonged in patients receiving lithium.	Caution should be exercised when the combination is required. A temporary omission of a few doses of lithium can reduce the risks of this interaction. Monitor for prolonged paralysis.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phenothiazines	C	Both pharmacokinetic interactions and clinical toxicity with the combined use of these agents have been described. Lithium-induced reductions in plasma chlorpromazine levels, phenothiazine-induced increases in the red cell uptake of lithium, and chlorpromazine-induced increases in renal lithium excretion have been reported. Clinically, occasional cases of neurotoxicity have been reported and may be more likely to occur with thioridazine than other phenothiazines when combined with lithium.	Clinicians should be alert for altered response to either drug when used in combination and when either drug is withdrawn.
Potassium Iodide	T	The hypothyroidic and goitrogenic effects of lithium carbonate and potassium iodide (and possibly other iodides) may be additive if the two drugs are used concurrently.	Monitor patients for signs or symptoms of hypothyroidism and goiter.
Propranolol	C	Limited clinical data suggests that propranolol may increase lithium serum concentrations, and its co-administration with lithium may produce bradycardia.	Pending further data, patients maintained on lithium should be monitored for changed lithium serum concentrations or exaggerated beta-blocker effects.
Selective Serotonin Reuptake Inhibitors (SSRI) Drugs (including fluvoxamine,	C and CT	Lithium may enhance the serotonergic effects of SSRI drugs. Coadministration of lithium with SSRI drugs may lead to a higher incidence of serotonin associated side	Combined use of lithium and SSRI drugs should be carried out with caution. Lithium levels should be monitored when these drugs are administered concomitantly, so

Proper/Common name	Source of Evidence	Effect	Clinical comment
fluoxetine, and sertraline)		effects (serotonin syndrome) and lithium toxicity. *Fluvoxamine:* Several cases of adverse reactions including convulsions have been reported in patients receiving concomitant lithium and fluvoxamine. *Fluoxetine:* There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported with coadministration of fluoxetine and lithium. *Sertraline*: In placebo-controlled study in normal volunteers sertraline did not alter steady-state concentrations or renal clearance of lithium. However, there was a high incidence of apparently treatment related side effects with the combination in this study, tremors being the most frequently observed. There is no clinical experience with lithium in sertraline treated patients.	that appropriate adjustments to the lithium dose may be made if necessary. 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.
Sodium Bicarbonate	T	Concomitant use can lower serum lithium concentrations by increasing urinary lithium	Patients on combined sodium bicarbonate and lithium

Proper/Common name	Source of Evidence	Effect	Clinical comment
		excretion.	therapy should be monitored for decreased lithium effects. Lithium blood levels may be helpful in assessing this interaction.
Thiazide diuretic	C	Patients stabilized on lithium therapy who receive a thiazide diuretic may require a reduction of lithium dosage to avoid accumulation and toxicity, since there is often a 20 to 40% reduction of renal lithium clearance. Furosemide appears to be less likely to affect lithium clearance.	Require a reduction of lithium dosage
Tricyclic Antidepressants	T	Both lithium and tricyclic antidepressants lower the seizure threshold. An additive effect is possible.	
Urea	C	Limited clinical experience indicates that urea may enhance the renal excretion of lithium resulting in reduced lithium serum concentrations.	More frequent serum lithium concentration monitoring.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Patients on salt-restricted diets who receive lithium are prone to developing symptoms of lithium toxicity. In contrast, increased sodium intake has been associated with reduced therapeutic response to lithium. Extremely large or small intakes of sodium chloride should be avoided in patients receiving lithium (see also 7 WARNINGS AND PRECAUTIONS, Renal).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The active ingredient in LITHMAX tablets is lithium carbonate.

Although lithium is useful for its anti-manic effect and in preventing relapses in patients with a clear-cut diagnosis of bipolar affective disorder, it has very little, if any, direct effect on moods, normal or abnormal.

Lithium alters sodium transport in nerve and muscle cells, effects a shift toward intraneuronal metabolism of catecholamines and has an inhibitory action on the intracellular formation of cyclic, AMP. However, the specific biochemical mechanism of action of lithium in mania is still largely unknown.

Use of a sustained-release lithium preparation can reduce the frequency of absorption-related side effects in selected individuals who are particularly sensitive to rapid increases in serum lithium concentrations.

10.2 Pharmacodynamics

Lithium is inactive in most psychopharmacological screening tests but it does produce marked potentiation of amphetamine hyperactivity in animals. It does not appear to protect against the action of stimulant and convulsive drugs and produces only slight potentiation of CNS depressants.

Lithium can replace sodium in extracellular fluid and during the process of depolarization it has an extremely rapid intracellular influx. However, it is not effectively removed by the sodium pump, thereby preventing the cellular re-entry of potassium. As a result, it interferes with electrolyte distribution across the neuronal membrane, leading to a fall in membrane potential and changes in conduction and neuronal excitability. In humans, lithium alters the excitability of the CNS as measured by cortical-evoked potentials.

Balance studies indicate that lithium may produce a transitory diuresis with increase in sodium and potassium excretion. A period of equilibrium or slight retention may follow but persistent polyuria may occur in some patients. There is evidence that therapeutic doses of lithium decrease the 24-hour exchangeable sodium. Longitudinal metabolic studies have demonstrated cumulative lithium retention in some patients without undue rise in plasma lithium values, indicating a possible intracellular retention of lithium. There is some evidence that lithium may affect the metabolism of potassium, magnesium and calcium.

There is also evidence to indicate that lithium might produce a shift in norepinephrine metabolism from O-methylation to intraneuronal deamination, as evidenced by a decrease in normetanephrine and an increase in deaminated catechols observed in animal studies. This would suggest that lithium may decrease levels of norepinephrine available at the central adrenergic receptors. It would appear, however, that this action is not specific of lithium. Lithium may also alter the metabolism of other monoamines such as serotonin (see 9.4 Drug-Drug Interactions, Table 3- Established or Potential Drug-Drug Interactions, Selective Serotonin Reuptake Inhibitors (SSRI) Drugs (including fluvoxamine, fluoxetine, and sertraline).

ECG changes with lithium have been reported in both animals and human.

The mechanism whereby lithium controls manic episodes and possibly influences affective disorders is not yet known.

Unlike other anti-manic agents, it does not possess general sedative properties. There is evidence, however, that lithium alters sodium transport and may interfere with the ion exchange mechanism and nerve conduction. Fluid and electrolyte metabolism are believed to be altered in affective disorders and this may be related to the therapeutic action of lithium. It also has been suggested that lithium may decrease norepinephrine levels at critical receptor sites in the brain where this catecholamine is presumed to be increased during mania.

10.3 Pharmacokinetics

Absorption

Information is not available.

Distribution

Information is not available.

Metabolism

Information is not available.

Elimination

Lithium is excreted primarily in the urine, and the elimination half-life is approximately 24 hours. Renal lithium clearance tends to be remarkably constant in the same individual but decreases with age or when sodium intake is lowered. The dose necessary to maintain a given concentration of serum lithium depends on the ability of the kidney to excrete lithium. However, renal lithium excretion may vary greatly between individuals, and lithium dosage, therefore, must be adjusted individually. It has been suggested that many patients retain larger amounts of lithium during the active manic phase but recent studies have been unable to confirm a clear difference in excretion patterns; however, patients in a manic state appear to have increased tolerance to lithium.

Special Populations and Conditions

- **Pediatrics (<12):** Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.
- **Geriatrics (>65 years of age):** Geriatrics patients often respond to reduced dosage and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients. See 4.2 Recommended Dose and Dosage Adjustment, Geriatrics.
- **Sex:** This information is not available for this drug product.
- **Pregnancy and Breast-feeding** The safe use of lithium carbonate during pregnancy and breast-feeding has not been established. It is unknown if lithium is excreted in human milk. See 7.1.1 Pregnant Women and 7.1.2 Breast-feeding.
- **Genetic Polymorphism:** The clinical trial data on which the indication was originally authorised is not available.
- **Ethnic Origin:** This information is not available for this drug product.

- **Hepatic Insufficiency:** This information is not available for this drug product.
- **Renal Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Renal.
- **Obesity:** This information is not available for this drug product.

11 STORAGE, STABILITY AND DISPOSAL

LITHMAX tablets should be stored between 15°C - 30°C.

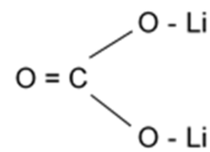
12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Lithium carbonate
Chemical name:	Carbonic acid, dilithium salt
Molecular formula and molecular mass	Li_2CO_3 and 73.89 g/mol
Structural formula:	
Physicochemical properties:	White, granular, odourless powder sparingly soluble in water, very slightly soluble in alcohol, dissolves with effervescence in dilute acid. Saturated solution is alkaline to litmus.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, two-way, single dose, crossover comparative oral bioavailability study of LITHMAX (Sustained-Release Tablets) 300mg (AA Pharma Inc) and PrDURALITH® Sustained-Release Tablets 300mg (Janssen-Ortho Inc.) was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from the 24 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lithium (2 x 300 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	95% Confidence Interval
AUC_T (mcg·h/mL)	46.09 47.56 (25.0)	42.20 43.22 (21.8)	109.2	99.5 – 119.9
AUC_{0-72} (mcg·h/mL)	51.79 52.52 (17.4)	46.01 46.54 (15.8)	112.8	104.6 – 121.7
AUC_I (mcg·h/mL)	51.34 53.00 (25.7)	46.84 48.05 (22.9)	109.6	100.3 – 119.8
C_{max} (mcg/mL)	1.98 2.01 (17.0)	1.92 1.93 (13.7)	103.4	96.3 – 111.0
T_{max}[3] (h)	5.00 (4.00-7.00)	4.00 (3.00-6.00)		
$T_{½}$[4] (h)	20.51 (21.1)	20.87 (20.7)		

[1] LITHMAX (lithium carbonate) Sustained-Release Tablets, 300 mg (AA Pharma Inc)
[2] prDURALITH®(lithium carbonate) Sustained-Release Tablets , 300 mg (Janssen-Ortho Inc)
[3] Expressed as the median (range) only .
[4] Expressed as the arithmetic mean (CV %) only

A randomized, two-way, single dose, crossover comparative oral bioavailability study of LITHMAX (Sustained-Release Tablets) 300mg (AA Pharma Inc) and prDURALITH® Sustained-Release Tablets 300mg (Janssen-Ortho Inc.) was conducted in healthy, adult male subjects under high-fat, high-calorie fed conditions. Comparative bioavailability data from the 24 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lithium (2 x 300 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	95% Confidence Interval
AUC_T (mcg·h/mL)	54.26 54.63 (11.6)	52.42 53.27 (16.5)	103.5	99.7 – 107.5
AUC_{0-72} (mcg·h/mL)	54.26 54.63 (11.6)	54.10 54.49 (12.1)	101.9	99.8 – 104.1
AUC_I (mcg·h/mL)	59.80 60.24 (12.1)	58.50 59.41 (16.4)	102.2	98.6 – 106.0
C_{max} (mcg/mL)	2.86 2.97 (28.2)	2.62 2.70 (26.2)	109.5	99.1 – 121.0
T_{max}[3] (h)	5.50 (3.00-9.00)	4.50 (3.00-12.00)		
$T_{½}$[4] (h)	21.77 (13.0)	22.6 (13.1)		

[1] LITHMAX (lithium carbonate) Sustained-Release Tablets, 300 mg (AA Pharma Inc.)
[2] PrDURALITH®(lithium carbonate) Sustained-Release Tablets , 300 mg (Janssen-Ortho Inc)
[3] Expressed as the median (range) only .
[4] Expressed as the arithmetic mean (CV %) only

A randomized, two-way, multiple dose, crossover comparative oral bioavailability study of LITHMAX (Sustained-Release Tablets) 300 mg (AA Pharma Inc.) and PrDURALITH® Sustained-Release Tablets 300mg (Janssen-Ortho Inc.), administered as 1 x 300 mg every 12 hours for 7 days, was conducted in healthy, adult male subjects under steady state fasting conditions. Comparative bioavailability data from the 24 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lithium (1 x 300 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	95% Confidence Interval
AUC_{tau} (mcg·h/mL)	34.51 35.12 (18.0)	32.52 33.07 (18.2)	106.1	101.7 – 110.7
C_{max} (mcg/mL)	3.46 3.52 (16.4)	3.33 3.37 (15.7)	104.1	100.1 – 108.3
C_{min} (mcg/mL)	2.16 2.23 (23.5)	2.02 2.08 (23.6)	107.1	101.1 – 113.4
T_{max}[3] (h)	4.00 (2.25-5.00)	4.00 (2.25-5.00)		
Fluctuation[4] (%)	45.18 (21.8)	48.32 (22.2)		

[1] LITHMAX (lithium carbonate) Sustained-Release Tablets, 300 mg (AA Pharma Inc.)
[2] prDURALITH®(lithium carbonate) Sustained-Release Tablets , 300 mg (Janssen-Ortho Inc)
[3] Expressed as the median (range) only .
[4] Expressed as the arithmetic mean (CV %) only

Special Studies

- A crossover multi-dose bioavailability study involving substituting lithium carbonate sustained-release tablets b.i.d. for regular lithium administered t.i.d. in the same total daily dosage for 5 days in manic patients previously stabilized with optimum therapeutic doses of regular-release lithium, showed that the area under the 24-hour plasma level curve (AUC) for lithium carbonate sustained-release tablets was 90% of that for the regular-release lithium. The peak for regular release lithium was 10 to 20% higher than that for sustained-release tablets ($p<0.01$) and the time to peak was greater for sustained-release tablets ($p<0.01$) compared to the regular-release product. The variability in plasma level over the 24-hour period was significantly greater (~40%) for the regular-release product compared to sustained-release tablets (the ratio of the ranges averaging 1.428:1, $p<0.01$).

  Furthermore, the number of hours during the 24-hour period in which the plasma level was in the toxic range (in excess of 1.5 mmol/L) was significantly higher for the regular-release tablet than for sustained-release tablets (2.31 hours regular lithium vs. 0.98 hours lithium carbonate sustained release tablets, $p<0.01$).

- In a double-blind crossover pharmacokinetic comparison study, sustained-release lithium carbonate (300 mg tablets) and regular-release lithium carbonate (300 mg capsules) were administered once a day for 2 weeks to patients with primary bipolar affective disorder who were previously stabilized at a constant dose of lithium. The study dosage for each patient was adjusted to be equal to the maintenance dose of the previous lithium medication. The plasma concentration-time curves from 10.5 to 23 hours post last-dose showed little difference either between the two treatments or between the order of treatment, and the lithium 'trough" levels were statistically similar after the 2 weeks of once-a-day lithium administration, for both treatments.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General toxicology

The acute oral LD_{50} of lithium carbonate in the rat is 635 mg/kg and in the mouse 650 mg/kg.

Subacute toxicity studies indicate that lithium accumulates faster, and death occurs earlier, in rats and dogs fed low sodium diets. Dogs given 20 mg/kg/day of lithium chloride showed no signs of toxicity when fed a normal salt diet, but died in 2-4 weeks when fed a low sodium diet. Similar results occurred in rats. The signs of toxicity consisted of tremors, lethargy, salivation, vomiting, diuresis, bloody diarrhea, anorexia, emaciation and coma. ECG changes similar to those produced by potassium intoxication were observed. Animals protected by a high sodium intake developed only polyuria. Serum lithium rose gradually in the animals developing signs of toxicity, while serum potassium levels remained fairly constant. In the final stages, serum lithium values rose rapidly as a result of irreversible renal damage, and in the terminal stages hyperkalemia and azotemia were recorded.

The principal toxic effects of lithium are on the kidney, with lesions in the distal convoluted tubules of dogs and in the proximal convoluted tubules of rats. The primary toxic effects in humans appear to be on the central nervous system.

The long-term toxicity of lithium has not yet been tested in animal studies.

Genotoxicity

Information is not available.

Carcinogenicity

Information is not available.

Reproductive and developmental toxicology

Lithium salts influenced the embryonal development of sea urchins, mollusks, amphibians and chicken embryos.

Adverse effects on reproduction have also been reported in mammalian species.

Adverse effects on the number of corpora lutea, percentage of resorptions, embryonic viability and weaning weight in rats, the number of implantation sites in rabbits and the birth weights in monkeys, have occurred in lithium studies. Cleft palate, together with ocular and auricular defects, occurred in the offspring of mice and rats treated with lithium at doses that produced blood levels similar to the therapeutic range in man.

Lithium decreases the fertility of male rats and is spermicidal *in vitro* for human and animal spermatozoa.

Juvenile Toxicity

Information is not available.

Special Toxicology

Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Duralith (Lithium Carbonate Sustained-Release Tablets), Product Monograph, Janssen-Ortho Inc. JUN 07, 1999

2. LITHANE (Lithium carbonate capsules USP), Product Monograph, Searchlight Pharma Inc., SEP 21, 2022

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrLITHMAX®

Lithium Carbonate Sustained-Release Tablets

This patient medication information is written for the person who will be taking LITHMAX. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about LITHMAX, talk to a healthcare professional.

Serious warnings and precautions box

- **Lithium toxicity:**
  - LITHMAX is a medicine for which small increases in dose or blood concentration can lead to lithium toxicity. It is also known as a lithium overdose. This means that toxic side effects can occur at doses close to the prescribed dose. Your healthcare professional will need to monitor your blood levels of lithium to find the best dose for you.
  - After a manic episode (a period of time where you have an abnormal amount of high energy), usually within a week, your healthcare professional may rapidly decrease your dose of LITHMAX. This is because your ability to tolerate LITHMAX may decrease after a manic episode and your usual dose may lead to a condition called lithium toxicity (a serious, life-threatening condition where there is too much lithium in your body).
- Stop taking LITHMAX and seek immediate medical help if you think you have taken too much LITHMAX or if you experience the following symptoms of lithium toxicity:
  - diarrhea
  - vomiting
  - shaking
  - lack of muscle control
  - drowsiness
  - muscular weakness

What LITHMAX is used for:

LITHMAX used to:

- treat manic episodes in adults who have a condition called manic-depressive disorder (also known as bipolar disorder). Signs of a manic episode include:
  - feeling invincible or an all-powerful inflated self-esteem,

- having racing thoughts, easily losing train of thought,
- overreacting to what you see or hear,
- speeding-up your activities,
- talking very quickly, too loudly, or more than usual,
- needing less sleep,
- having poor judgment,
- severe irritability.

- prevent or reduce further mood swings, either up (mania) or down (depression) in adults with manic-depressive disorders (bipolar disorder).

How LITHMAX works:

LITHMAX belongs to a group of medicines called antimanic agents. It works by stabilising the chemicals in your brain that affect your mood.

The ingredients in LITHMAX are:

Medicinal ingredients: Lithium carbonate.

Non-medicinal ingredients: Hydroxypropyl methylcellulose and magnesium stearate.

LITHMAX comes in the following dosage form:

Sustained-Release Tablets: 300 mg.

Do not use LITHMAX if:

- you are allergic to lithium carbonate, any of the ingredients in LITHMAX or any part of the container (see **The ingredients in LITHMAX are**).
- you have or have had severe brain damage.
- you have or have had kidney problems
- you have or have had heart problems, an abnormal heart beat or heart disease.
- you have a condition that causes severe weakness or frailty.
- you are severely dehydrated.
- have been told you have low levels of salt (sodium) in your blood or are on a diet low in salt (sodium).
- you are taking medicines called diuretics that increase urine production.
- you are under 12 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LITHMAX. Talk about any health conditions or problems you may have, including if you:

- have impaired renal function.
- have or have had thyroid or parathyroid problems.
- have been told that you have high levels of calcium in your blood.
- suffer from excessive vomiting, diarrhea, or sweating.
- are pregnant, think you might be pregnant or planning to become pregnant.
- are breastfeeding.
- are 65 years of age or older.

Other warnings you should know about:

- **LITHMAX may cause serious side effects such as:**

  - **Encephalopathic syndrome (a brain disorder):** Cases of encephalopathic syndrome have been seen in patients taking lithium with a medicine called haloperidol (antipsychotic medicine used to treat mental and emotional disorders). This condition can lead to permanent brain damage. Your healthcare professional will monitor you if you are taking LITHMAX with any antipsychotic medicines.

  - **Thyroid problems:** The thyroid is a butterfly-shaped gland located at the front of your neck. LITHMAX can cause an enlarged thyroid (also known as goiter). Tell your healthcare professional if you notice your thyroid getting bigger while taking LITHMAX. They may prescribe treatment with small doses of thyroid hormones to help stop further growth or shrink your thyroid. If you have taken LITHMAX for a long time, the enlarged thyroid may disappear on its own after you stop taking LITHMAX.

  - **Hypercalcemia** (high blood calcium): Taking LITHMAX for a long time may cause high levels of calcium in the blood. This can also be accompanied with a hormone disorder called hyperparathyroidism. This is a condition where your parathyroid glands (located behind your thyroid gland), create too much parathyroid hormone in the blood. This could lead to other medical problems.

  - **Kidney problems:** LITHMAX may cause frequent urination and other kidney problems that may affect how the kidneys work. This may occur in patients taking LITHMAX for a long time.

  - **Serious skin reactions**: LITHMAX may cause a condition called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This is a serious condition where you experience a skin rash that spreads to large areas of your body. You may also experience a fever, swelling of the face, inflammation of major organs like your kidneys or liver and swollen lymph nodes (small organs in your body that are part of your immune system and contain white blood cells to help fight infections).

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects

- **Driving and using machines**: Be careful about driving, operating machines, or doing activities that require you to be alert. LITHMAX may impair your mental and physical abilities. If you experience this while using LITHMAX, you should not drive or operate machines.
- **Diet and hydration:** LITHMAX may decrease salt (sodium) levels in your body. Therefore, it is important to have a consistent and normal diet consuming enough salt and water.
  - Do not make any sudden changes to your diet or salt (sodium) intake. Talk to your healthcare professional before making any changes.
  - If you are exercising for a long period of time or have been suffering from excessive vomiting, sweating or diarrhea, drink plenty of fluids.
  - Low salt levels and dehydration may affect the amount of lithium in your blood. This could lead to toxic levels of lithium in your blood.
  - If you experience conditions that could lead to low salt levels in your blood and/or dehydration (for example, sweating, diarrhea, infections, fevers, etc.) you may have to stop taking LITHMAX. Talk to your healthcare professional if you experience these conditions.
- **Pregnancy and birth control:**
  - LITHMAX should not be used by women who are pregnant or could be come pregnant.
  - Tell your healthcare professional right away if you become pregnant or think you might be pregnant while taking LITHMAX. They will discuss the treatment and risks with you and decide if you should continue taking LITHMAX.
  - Women who are able to get pregnant should have a pregnancy test done before starting treatment with LITHMAX and should avoid becoming pregnant during treatment.
  - You should use birth control while taking LITHMAX whether you are male or female.
- **Breast-feeding**
  - LITHMAX can pass into breast milk and harm your child. LITHMAX should not bet used while breast-feeding. Your healthcare professional will decide if treatment with LITHMAX outweighs the risk in these cases.
- **Adults (65 years of age or older):**
  - You may be more likely to experience a side effect, called lithium toxicity (a serious, life-threatening condition where there is too much lithium in your body), while taking LITHMAX. This can happen even at doses prescribed for you. Your healthcare professional may start you with a lower dose of LITHMAX and see how you respond to it.

- **Check-ups and testing:** Your healthcare professional may do check-ups and tests before you start LITHMAX and during your treatment. These tests may include:
    - blood tests to monitor:
        - the amount of lithium in your blood
        - the health of your kidneys, thyroid and parathyroid glands
        - the electrolyte levels (sodium and calcium) in your blood
    - urine tests to monitor:
        - your hydration level
        - the health of your kidneys
    - electrocardiogram (ECG) tests to monitor the health of your heart.
    - body weight checks to monitor any weight gain.
    - mental status checks to monitor your mental health.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LITHMAX:

- medicines used to treat high blood pressure or other heart problems such as:
    - thiazide diuretics, (also known as “water pills”) like furosemide.
    - Angiotensin Converting Enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril or lisinopril).
    - calcium channel blockers (e.g., verapamil, diltiazem, amlodipine, felodipine, nifedipine).
    - a beta blocker like propranolol.
    - methyldopa.
- medicines used to treat asthma and other lung diseases like aminophylline or theophylline.
- medicines used to treat fits or seizures like carbamazepine or phenytoin.
- medicines used to treat serious mental and emotional disorders, including schizophrenia and other psychotic disorders. These include:
- haloperidol
- phenothiazines (like as prochlorperazine, chlorpromazine, thioridazine, perphenazine, fluphenazine).
- medicines used in anaesthesia (preventing the feeling of pain during medical procedures) called neuromuscular blocking agents.
- medicines called non-steroidal anti-inflammatory agents (NSAIDs) that are used to relieve pain and reduce inflammation like indomethacin, ibuprofen, naproxen, diclofenac and celecoxib.
- tetracyclines (used to treat infections).
- diets that are low in salt (sodium).
- mazindol (used to supress appetite).
- urea (used to treat low levels of salt (sodium) in the blood).

- sodium bicarbonate (used to reduce stomach acid and treat heartburn).
- diazepam (used to treat anxiety, alcohol withdrawal and seizures).
- potassium iodide (used to treat an overactive thyroid and to protect the thyroid gland from the effects of radiation).
- medicines used to treat depression, like selective serotonin reuptake inhibitors (SSRI) (such as fluvoxamine, fluoxetine, citalopram and sertraline) or tricyclic antidepressants.
- medicines used to cause short-term paralysis during surgery (like succinylcholine and pancuronium).

How to take LITHMAX:

- Take LITHMAX exactly as your healthcare professional has told you.
- Swallow the whole tablet or half-tablet (if broken in half).
- Do NOT chew or crush the tablets.
- Do NOT take more LITHMAX than you are told by your healthcare professional. This may cause you serious harm or even death.

Usual dose:

- Your healthcare professional will tell you how much and how often to take LITHMAX. How much you take will depend on your condition.
- During your treatment, your healthcare professional will check if LITHMAX is working for you and if it is causing you any unwanted side effects.
- They may change how much LITHMAX you take depending on the amount of lithium in your blood and how your respond to LITHMAX.
- After a manic episode (usually within a week), your healthcare professional may rapidly decrease how much LITHMAX you take. This is to avoid unwanted side effects.

Overdose:

Signs of an overdose with LITHMAX may include:

- feeling sluggish,
- drowsiness
- lack of energy,
- shaking, or muscle or twitching,
- loss of appetite, vomiting,
- diarrhea.

If you experience these symptoms, STOP taking LITHMAX immediately and talk to your healthcare professional.

If you think you, or a person you are caring for, have taken too much LITHMAX, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, skip the missed dose and take your next dose at the usual time.

Possible side effects from using LITHMAX:

These are not all the possible side effects you may have when taking LITHMAX. If you experience any side effects not listed here, tell your healthcare professional.

- nausea
- vomiting
- diarrhea
- dry mouth
- stomach pain
- loss of appetite
- tiredness, weakness
- blind spots in your eyesight
- weight changes
- repeated jerking movements of the arms and legs on one or both sides of the body, sometimes with numbness or tingling.
- headache
- worsening of a condition called organic brain syndrome. This is a condition that affects your brain and impacts you're your mental abilities like memory, thinking, attention and perception.
- metallic taste in your mouth
- feeling thirsty or dehydrated
- vertigo (feeling like you are spinning)
- painful discoloration of fingers and toes, cold hands, and feet
- problems with kidney function, bones and skin

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Gastrointestinal disorders: Nausea, abdominal pain, vomiting, diarrhea, anorexia (eating disorder that causes very low body weight and obsession about weight and what you eat)	√		

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Nervous system disorders: Reduced awareness of the environment, muscle weakness, sleepiness, a dazed feeling (unable to think clearly), hand tremor	√		
General disorders: Abnormally increased thirst and polyuria (larger than usual urine volumes), fatigue, vertigo	√		
RARE			
Hyperthyroidism (high thyroid hormone): anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly feelings of having rapid, fluttering or pounding heart, feeling shakey, increased appetite, excessive sweating, vision changes, menstrual changes.		√	
UNKNOWN			
Blood and lymphatic system disorders: elevated white blood cell count		√	
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		√	
Endocrine disorders: Thyroid problem and the condition known as Euthyroid goiter (enlarged thyroid gland), hypothyroidism (including myxedema): lower T_3 and T_4 levels and elevated TSH, weight loss or weight gain		√	
Eye Disorders: Blurred vision, visual field defect (blind spot, partial loss of vision)	√		
Gastrointestinal disorders: Dry mouth, loss of appetite, metallic taste, vomiting	√		
General disorders: Loss of full control of body movement, lethargy, fatigue	√		
Metabolism and nutrition disorders: Loss of appetite, dehydration	√		
Enlargement of the thyroid gland (with or without hypothyroidism): elevated level of the sugar glucose in the blood		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Musculoskeletal and connective tissue disorders: Muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), swelling of ankles or wrists		√	
Nervous system disorders: tremor, muscle hyperirritability (fasciculation, twitching, especially of facial muscles and clonic movements of the limbs), hypertonicity, ataxia, choreoathetotic movement, hyperactive deep tendon reflexes, extrapyramidal symptoms including acute dystonia and parkinsonism, general muscle weakness, urinary and fecal incontinence, slurred speech, blackout spells, seizures, cranial nerve involvement, psychomotor retardation, somnolence, dizziness, toxic confusional states, restlessness, stupor, coma, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes, myasthenic syndromes		√	
Psychiatric disorder: Slurred speech, state of being drowsy, slowing down or inhibition of mental and physical activity, state of near-unconsciousness or insensibility, tendency to sleep, confusion		√	
Renal and urinary disorders: Increased albumin in urine, decreased or increased urination (resembling diabetes insipidus), glucose in urine.		√	
Skin and subcutaneous tissue disorders: Drying and thinning of hair, loss of sensation of skin, acne, inflammation of hair follicles in skin, abnormally dry skin, alopecia and red, itchy scaly patches, most commonly on the knees, elbows, trunk and scalp, pruritis, cutaneous ulcers	√		

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect one or more organs): fever, severe rash, peeling skin, swelling of the face or legs, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine or dark urine.		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	√		
Peripheral circulatory collapse (the body is unable to circulate blood to the organs): low blood pressure, rapid heart rate, pale cool clammy skin, rapid breathing, confused or altered mental status, weakness or dizziness, loss of consciousness.This is very serious and can lead to death.			√
Encephalopathic syndrome (a rare neurological disorder): feeling weak, extreme sleepiness, fever, trembling, confusion, inability to sit still, involuntary muscle contraction or facial movements, shaking, or stiff muscles, can lead to permanent brain damage.			√
Hypercalcemia (high blood calcium): constipation, weight loss, nausea, vomiting, abdominal pain, loss of appetite. Can be accompanied with body aches, sleepiness or difficulty sleeping, bone pain, memory loss, poor concentration, depression, or headache.		√	
Lithium toxicity (lithium overdose): upset stomach, diarrhea, vomiting, feeling thirsty, lack of coordination, muscle control or energy, shaking, muscle weakness, sleepiness, ringing in the ears, blurry vision, confusion, feeling disoriented, muscle twitching, lack of reflexes,			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
involuntary eye movements (side to-side, up and down, or circular motion of the eyes), seizures, coma, death.			
Thyroid problems: enlarged thyroid gland, weight changes, tiredness, anxiety or nervousness, hair loss, muscle weakness, feeling cold, dry skin, constipation or frequent and loose bowel movements, shortness of breath, puffy face, heavier than normal or irregular menstrual periods, feeling hot and possibly feelings of having rapid, fluttering or pounding heart.		√	
Pseudotumor cerebri (increased pressure in the skull): severe headache, ringing in the ears, blurred vision, double vision or brief periods of blindness.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store LITHMAX tablets between 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about LITHMAX:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

Last Revised: APR 01, 2025