LITHIUM CARBONATE - lithium carbonate tablet, extended release
West-ward Pharmaceutical Corp.

Rev. 04/07
Rx Only

WARNING

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

DESCRIPTION
Lithium Carbonate is a white, light alkaline powder with molecular formula Li_2CO_3 and molecular weight 73.89. Lithium is an element of the alkali-metal group with atomic number 3, atomic weight 6.94 and an emission line at 671 nm on the flame photometer. Each extended-release tablet for oral administration contains 450 mg of lithium carbonate. In addition, each tablet contains the following inactive ingredients: Alginic Acid, Corn Starch, Magnesium Stearate, Povidone, and Yellow Iron Oxide. Lithium Carbonate Extended-Release Tablets 450 mg are designed to release a portion of the dose initially and the remainder gradually; the release pattern of the extended release tablets reduces the variability in lithium blood levels seen with the immediate release dosage forms. This product meets USP Drug Release Test 2.

CLINICAL PHARMACOLOGY
Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown.

INDICATIONS AND USAGE
Lithium carbonate is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.
Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness and possibly hostility. When given to a patient experiencing a manic episode, *lithium carbonate* may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS
Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.
Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.
Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established.
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 following a period of water deprivation, 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 reevaluation of treatment.
An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).
Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels (see **DOSAGE AND ADMINISTRATION**).
Outpatients and their families should be warned that the patient must discontinue lithium carbonate therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness or muscular weakness occur.
Lithium carbonate may impair mental and/or physical abilities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.
Pregnancy: Adverse effects on implantation in rats, embryo viability in mice and metabolism *in vitro* of rat testes and human spermatozoa have been attributed to lithium, as have teratogenicity in subman-nalian species and cleft palates in mice.
In humans, lithium carbonate may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly.
If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the child.
Pediatric Use: Since information regarding the safety and effectiveness of lithium carbonate in children under 12 years of age is not available, its use in such patients is not recommended.
There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.
Geriatric Use: Elderly patients often require lower lithium dosages to achieve therapeutic serum levels. They may also exhibit adverse reactions at serum levels ordinarily tolerated by younger patients.

PRECAUTIONS

General:
The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see **DOSAGE AND ADMINISTRATION**).
The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-life of elimination of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (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 such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.
In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.
Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; where hypothyroidism 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.

Drug Interactions:
Caution should be used when lithium and diuretics are used concomitantly because diuretic-induced sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary.
Lithium levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly, steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxgenase-2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg b.i.d. with celecoxib 200 mg b.i.d. as compared to subjects receiving lithium alone.
Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.
There is evidence that angiotensin-converting enzyme inhibitors, such as enalapril and captopril, and angotension II receptor antagonists, such as losartan, may substantially increase steady-state plasma lithium levels, sometimes resulting in lithium toxicity. When such combinations are used, lithium dosage may need to be decreased, and plasma lithium levels should be measured more often.
Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or tinnitus. Caution is recommended.
The concomitant administration of lithium with selective serotonin reuptake inhibitors should be undertaken with caution as this combination has been reported to result in symptoms such as diarrhea, confusion, tremor, dizziness and agitation.
The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.
The following have also been shown to interact with lithium: methyldopa, phenytoin and carbamazepine.

ADVERSE REACTIONS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual patient sensitivity to lithium, and generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium levels below 1.5 mEq/L. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq/L, and moderate to severe reactions may be seen at levels of 2.0 mEq/L and above.

Fine hand tremor, polyuna and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration. These side effects usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, cessation of lithium therapy may be required.

Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq/L. At higher levels, ataxia, giddiness, tinnitus, blurred vision and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq/L may produce a complex clinical picture, involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

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

Neuromuscular/Central Nervous System - tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus; hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes, myasthenia gravis (rarely);

Cardiovascular – cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope);

Gastrointestinal - anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion;

Genitourinary - glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia;

Dermatologic - drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without, rash, cutaneous ulcers, angioedema;

Autonomic - blurred vision, dry mouth, impotence/sexual dysfunction;

Thyroid Abnormalities - euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4. I131 uptake may be elevated. (See **PRECAUTIONS**.) Paradoxically, rare cases of hyperthyroidism have been reported;

EEG Changes - diffuse slowing, widening of the frequency spectrum, potentiation and disorganization of background rhythm;

EKG Changes -reversible flattening, isoelectricity or inversion of T-waves;

Miscellaneous - fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received 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.

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.

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 toxic symptoms and to discontinue the drug and inform the physician should they occur. Toxic symptoms are listed in detail under **ADVERSE REACTIONS.**

Treatment

No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient. Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance, and 3) regulation of kidney function. Urea, mannitol and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. Infection prophylaxis, regular chest X-rays and preservation of adequate respiration are essential.

DOSAGE AND ADMINISTRATION

Doses of extended-release tablets are usually given b.i.d. (approximately 12-hour intervals). When initiating therapy with extended-release lithium, dosage must be individualized according to serum levels and clinical response.

When switching a patient from immediate-release capsules to the lithium carbonate extended-release tablets, give the same total daily dose when possible. Most patients on maintenance therapy are stabilized on 900 mg daily, e.g., 450 mg lithium carbonate extended-release b.i.d. When the previous dosage of immediate-release lithium is not a multiple of 450 mg, for example, 1500 mg, initiate lithium extended-release tablet at the multiple of 450 mg nearest to, but *below*, the original daily dosage, i.e., 1350 mg. When the two doses are unequal, give the larger dose in the evening. In the above example, with a total daily dosage of 1350 mg, generally 450 mg lithium carbonate extended-release should be given in the morning and 900 mg lithium carbonate extended-release in the evening.

If desired, the total daily dosage of 1350 mg can be given in three equal 450 mg lithium carbonate extended-release doses. These patients should be monitored at 1 to 2 week intervals, and dosage adjusted if necessary, until stable and satisfactory serum levels and clinical state are achieved.

When patients require closer titration than that available with doses of lithium carbonate extended-release in increments of 450 mg, immediate-release capsules should be used.

Acute Mania - Optimal patient response to lithium carbonate can usually be established and maintained with 1800 mg per day in divided doses. Such doses will normally produce the desired serum lithium level ranging between 1 and 1.5 mEq/L.

Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

Long-Term Control - The desirable serum lithium levels are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually 900 mg to 1200 mg per day in divided doses will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months.

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

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

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

HOW SUPPLIED

Lithium Carbonate Extended-Release Tablets USP, 450 mg are supplied as Yellow, Round Tablets, Scored on one side and Imprinted “WW 277” on the other side and are available in:

Bottles of 30 tablets.

Bottles of 90 tablets.

Bottles of 100 tablets.

Bottles of 500 tablets.

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature].

Manufactured By:

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