LITHIUM CARBONATE- lithium carbonate tablet, extended release
A-S Medication Solutions

Lithium Carbonate Extended-Release Tablets USP, 450 mg

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 Extended-release Tablets USP contain lithium carbonate USP, a white granular 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.

Lithium Carbonate Extended-release Tablets USP are available for oral administration containing 450 mg of lithium carbonate USP. Each tablet contains the following inactive ingredients: sodium alginate, sodium starch glycolate, povidone, ferric oxide yellow, magnesium stearate.

Lithium Carbonate Extended-release Tablets USP, 450 mg are designed to release a portion of the dose initially and the remainder gradually; the release pattern of the controlled release tablets reduces the variability in lithium blood levels seen with immediate release dosage forms.

The tablets comply with USP 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 maniac-depressive illness. Maintenance therapy revents or diminishes the intensity of subsequent episodes in those maniac-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 Toxicity

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic

concentrations (see **DOSAGE AND ADMINISTRATION**).

Outpatients and their families should be warned that the patient must discontinue lithium 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 patiens about activities required alertness (e.g., operating vehicles or machinery).

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 patients fails to respond to other measeures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustmen to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Unmasking of Brugada Syndrome

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

Renal Effects

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

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, creatinine clearance or proteinuria). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for re-evaluation of treatment.

Encephalopathic Syndrome

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events

and the concomitant administration of lithium and 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).

Concomitant Use with Neuromuscular Blocking Agents

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

Usage in Pregnancy

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

Usage in 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 hazard to the child.

Usage in Pediatric Patients

Since information regarding the safety and effectiveness of the lithium carbonate in children under 12 years of age is not availabel, its use in such patients is not recommended.

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

Usage in the Elderly

Elderly patients often require lower lithium dosages to acheive 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 3500 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been

reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters, if any; where hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

Information for Patients

A condition known as Brugada Syndrome may pre-exist and be unmasked by lithium therapy. Brugada Syndrome is a heart disorder characterized by abnormal electrocardiographic (ECG) findings and risk sudden death. Patients should be advised to seek immediate emmergency assistance if they experience fainting, lightheadedness, abnormal heart beats, or shortness of breath.

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 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 a NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with celecoxib 200 mg BID as compared to subjects receiving lithium alone.

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 angiotensin 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 dodium bicarbonate.

The following have also been shown to interact with lithium: methyldopa, phenytoin and carbamazapine.

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 concentrations 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 concentrations from 2 mEq/L and above.

Fine hand tremor, polyuria, 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, a 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 mEq/L. At higher levels, giddiness, ataxia, blurred vision, tinnitus, and a large output of dilute urine may be seen. Serum lithium concentrations above 3 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations should not be permitted to exceed 2 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), Unmasking of Brugada Syndrome (see **WARNINGS: Unmasking of Brugada Syndrome** and **PRECAUTIONS: Information for the patients**).

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 T3 and T4. ^{131}I uptake may be elevated (see **PRECAUTIONS**). Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes: diffuse slowing, widening of 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, and 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 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) may have been reported with lithium use. If undected, this condition may result in enlargement of the blind spot, constriction of visula fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

OVERDOSAGE

The toxic concentrations 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 functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. 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 immediate-release or extended-release lithium, dosage may be individualized according to serum levels and clinical response.

When switching a patient from immediate-release capsules to the lithium carbonate extended-release tablets USP, give the same total daily dose when possible. Most patients on maintenance therapy are stabilized on 900 mg daily, e.g., lithium extended-release tablets. 450 mg, b.i.d. When the previous dosaqge of immediate-release lithium is not a multiple of 450 mg, e.g., 1500 mg, initiate lithium extended-release tablet at the multiple of 450 mg nearest to, byt below, the original daily dose, 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 dose of 1350 mg, generally 450 mg of lithium carbonate extended-release tablets should be given in the morning and 900 mg of lithiumcarbonate extended-release tablets in the evening. If desired, the total daily dose of 1350 mg can be given in three parts of 450 mg doses of lithium carbonate extended-release tablets. Thses patients should be monitored at 1- to 2-week intervals, and dosage adjusted if necessary, until stable and satisfactory serum levels and clinican state is acheived.

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

Acute Mania

Optimal patient response can usually be established and maintained with 1800 mg/day in divided doses. Such doses will normally produce an effective serum lithium concentration ranging between 1 and 1.5 mEq/L.

Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and of 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

Desirable serum lithium concentrations are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually 900 to 1200 mg/day generally in divided dosages will maintain this level. Serum lithium levels 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 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 previous dose). Total reliance must not be placed on serum concentrations alone. Accurate patient evaluation requires both clinical and laboratory analysis.

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

HOW SUPPLIED

Product: 50090-3490

NDC: 50090-3490-0 33 TABLET, EXTENDED RELEASE in a BOTTLE

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C [See USP Controlled Room Temperature.] Protect from moisture. Dispense in tight, child-resistant container USP/NF.

Lithium Carbonate

LITHIUM CARBONATE

lithium carbonate tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50090-3490(NDC:64980-278)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LITHIUM CARBONATE (UNII: 2BMD2GNA4V) (LITHIUM CATION - UNII:8H8Z5UER66)	LITHIUM CARBONATE	450 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM ALGINATE (UNII: C269C4G2ZQ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	white (white to Off White)	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	P;450
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:50090-3490-0	33 in 1 BOTTLE; Type 0: Not a Combination Product	06/18/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205663	12/01/2017	

Labeler - A-S Medication Solutions (830016429)

Establishment

Name	Address	ID/FEI	Business Operations
A-S Medication Solutions		830016429	RELABEL(50090-3490) , REPACK(50090-3490)

Revised: 6/2018 A-S Medication Solutions