

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**76170**

**DRAFT FINAL PRINTED LABELING**

SAMPLE

APPROVED



LITHIUM CARBONATE  
EXTENDED-RELEASE TABLETS, USP



Revised APRIL 2002  
1603450102

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JUN 10 2002

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.

**DESCRIPTION:**

Lithium Carbonate Extended-Release Tablets are a form of an antimanic medication for oral administration. Each off-white, film-coated, extended-release tablet contains 300 mg of lithium carbonate. This slowly dissolving, film-coated tablet is designed to give lower serum lithium peaks than obtained with conventional oral lithium dosage forms. Lithium carbonate, USP is a white, granular, odorless powder, which is sparingly soluble in water and very slightly soluble in alcohol. It dissolves, with effervescence, in dilute mineral acids. Its molecular formula is  $\text{Li}_2\text{CO}_3$  and molecular weight is 73.89.

The inactive ingredients are as follows: calcium stearate, carnauba wax, hydroxypropyl methylcellulose, methylcellulose, polyethylene glycol, polydioxane, sodium starch glycolate, and sorbitol.

This Product meets USP Drug Release Test 1.

**INDICATIONS AND USAGE:**

Lithium 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 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, dehydration, or sodium depletion, and to patients receiving diuretics, 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.

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to the therapeutic levels (see DOSAGE AND ADMINISTRATION). Lithium therapy has been reported in some cases to be associated with morphologic changes in the kidneys. The relationship between such changes and renal function has not been established. 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 may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Lithium may impair mental and/or physical abilities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

**Combined use of haloperidol and lithium:** An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leucocytosis, elevated serum 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 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 neurological toxicity and treatment discontinued promptly if such signs appear. The possibility of similar adverse interactions with other antipsychotic medications exists.

**PRECAUTIONS:**

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-elimination time 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 (2500-3000 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. In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying 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.

Indomethacin (50 mg I.I.d.) has been reported to increase steady-state plasma lithium levels from 30 to 59 percent. There is also some evidence that other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased plasma lithium level monitoring is recommended.

**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 sub-mammalian species and cleft palate in mice. Studies in rats, rabbits and monkeys have shown no evidence of lithium-induced teratology.

There are lithium birth registries in the United States and elsewhere; however, there are at the present time insufficient data to determine the effects of lithium on human fetuses. Therefore, at this point, lithium should not be used in pregnancy, especially the first trimester, unless in the opinion of the physician, the potential benefits outweigh the possible hazards.

**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 in children under 12 years of age is not available, its use in such patients is not recommended at this time.

**ADVERSE REACTIONS:**

Adverse reactions are seldom encountered at serum lithium levels below 1.5 mEq/L, except in the occasional patient sensitive to lithium. Mild to moderate toxic reactions may occur at levels from 1.5-2.5 mEq/L, and moderate to severe reactions may be seen at levels from 2.0-2.5 mEq/L, depending upon individual response to the drug.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy

(over)

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 are an inconvenience rather than a disabling condition, and usually subside with continued treatment or with a temporary reduction or cessation of dosage. If persistent, a cessation of dosage is indicated.

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, giddiness, ataxia, blurred vision, tinnitus 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 toxic reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range:

**Neuromuscular:**

Tremor, muscle hyperirritability (tastulations, twitching, clonic movements of whole limbs), ataxia, choreoathetotic movements, hyperactive deep tendon reflexes.

**Central Nervous System:**

Blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma. 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. If this syndrome occurs, lithium should be discontinued, if clinically possible.

**Cardiovascular:**

Cardiac arrhythmia, hypotension, peripheral circulatory collapse.

**Gastrointestinal:**

Anorexia, nausea, vomiting, diarrhea.

**Genitourinary:**

Albuminuria, oliguria, polyuria, glycosuria.

**Dermatologic:**

Drying and thinning of hair, anesthesia of skin, chronic folliculitis, xerosis cutis, alopecia, exacerbation of psoriasis.

**Autonomic Nervous System:**

Blurred vision, dry mouth.

**Miscellaneous:**

Fatigue, lethargy, tendency to sleep, dehydration, weight loss, transient scotomata.

**Thyroid Abnormalities:**

Euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower  $T_3$  and  $T_4$ .  $I_{131}$  iodine 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 Reactions Unrelated to Dosage are:**

Transient electroencephalographic and electrocardiographic changes, leukocytosis, headache, diffuse nontoxic goiter with or without hypothyroidism, transient hyperglycemia, generalized pruritus with or without rash, cutaneous ulcers, albuminuria, worsening of organic brain syndromes, excessive weight gain, edematous swelling of ankles or wrists, and thirst or polyuria, sometimes resembling diabetes insipidus and metallic taste.

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

**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 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:****Acute Mania:**

Optimal patient response can usually be established and maintained with the following dosages:  
900 mg b.i.d. or 600 mg t.i.d. (1800 mg per day).

Such doses will normally produce an effective serum 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 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:**

The desirable serum lithium levels are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually the following dosages will maintain this level.

900 mg to 1200 mg per day given in two or three divided doses.

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 levels of 1 to 1.5 mEq/L. Elderly 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 determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e., 8-12 hours after previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

Lithium Carbonate Extended-Release Tablets must be swallowed whole and never crushed or chewed.

**HOW SUPPLIED:**

Lithium Carbonate Extended-Release Tablets, USP are available as:  
300 mg: Off-white, round, film-coated, biconvex, unscored tablets.  
Debossed with 6 on one side and 345 on the other side.  
100 NDC 0555-0345-02  
1000 NDC 0555-0345-06

Dispense with a child-resistant closure in a tight container.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Protect from moisture.

MANUFACTURED BY  
BARR LABORATORIES, INC.  
POMONA, NY 10970

Revised APRIL 2002  
BR-345

**Each tablet contains:**  
 Lithium Carbonate, USP 300 mg  
 This product meets USP  
 Drug Release Test 1.  
**DOSAGE AND ADMINISTRATION:**  
 See package brochure.  
**WARNINGS:**  
 See package brochure.  
 Dispense with a child-resistant  
 closure in a tight container.  
 Store at controlled room temper-  
 ature 15°-30°C (59°-86°F) [See USP].  
 Protect from moisture.

BARR LABORATORIES, INC.

NDC 0555-0345-05



**Lithium Carbonate  
 Extended-Release  
 Tablets, USP**

**300 mg**

**Rx only**

**1000 Tablets**



Exp:  Lot: SAMPLE

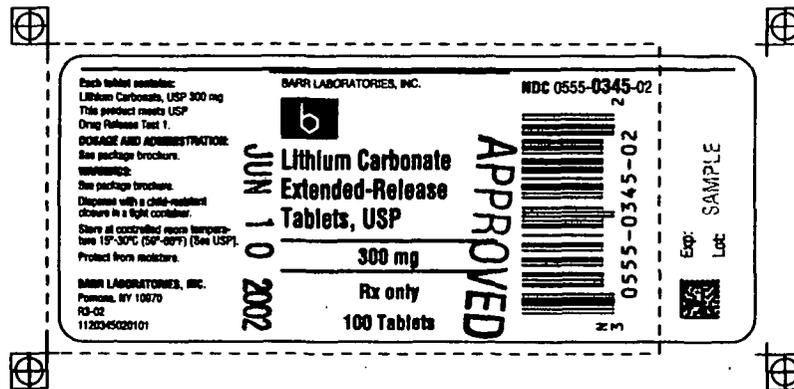
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JUN 10 2002

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Art #: 233734 OL		Order #: 87127		Proof is at 100%		Holding lines do not print	
Date	Authorized Signature	Colors: (PMS Swatch on proof does not represent exact color.)					
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Art #: 233738 OL		Order #: 87131			<input type="checkbox"/> Press Proof			
Date	Authorized Signature	Colors: (PMS Swatch on proof does not represent exact color.)		Proof Date	03/14/02	03/12/02		
		<input type="checkbox"/> PMS 293 <input type="checkbox"/> PMS 360 <input type="checkbox"/> BLACK		Version No.	1	2		
<input type="checkbox"/> Proof Approval <input type="checkbox"/> Reproof Required				Operator	RWP/SH	JA		
				Code Specs	UPC CODE: Mag.: 85% BWR: -.0005 DATAMATRIX CODE: ECC: 070 Scans as: 1120345020101			