PRODUCT MONOGRAPH

[Pr]APO-LITHIUM CARBONATE

Lithium Carbonate Capsules USP
150 and 300 mg

Antimanic Agent

APOTEX INC.
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Control # 170001

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PRODUCT MONOGRAPH

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Lithium Carbonate Capsules USP
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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.

Kinetics:

Lithium ions are rapidly absorbed from the gastrointestinal tract and plasma lithium peaks are reached two to four hours after lithium administration. The distribution of lithium in the body approximates that of total body water, but its passage across the blood-brain barrier is slow and at equilibration the CSF lithium level reaches only approximately half the plasma concentration.

Lithium undergoes a biphasic elimination pathway with an alpha half-life of 5 hours and beta half-life of 18 hours.

Lithium is excreted primarily in urine with less than 1% being eliminated with the feces. Lithium is filtered by the glomeruli and 80% of the filtered lithium is reabsorbed in the tubules, probably by the same mechanism responsible for sodium reabsorption.

The renal clearance of lithium is proportional to its plasma concentration. About 50% of a single dose of lithium is excreted in 24 hours. A low salt intake resulting in low tubular concentration of sodium will increase lithium reabsorption and might result in retention or intoxication.

Renal lithium clearance tends to be remarkably constant in the same individual but decreases with age and 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 must, therefore, be adjusted individually. In clinical reports, it has been noted that serum lithium may rise an average of 0.2 to 0.4 mEq or mmol/L after intake of 300 mg and 0.3 to 0.6 mEq or mmol/L after intake of 600 mg of lithium carbonate. It has been suggested that manic 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 seem to have an increased tolerance to lithium.

Once daily administration:

Clinical trials comparing once daily at bedtime dosing versus 2-4 times-a-day dosing have shown that urinary volume is significantly decreased with single daily dosing.

Total daily doses of lithium required to reach therapeutic levels were lower with the once-daily dosage schedule than with the divided dosage schedule.

In addition, administration of a single bedtime dose of lithium may result in initial post-absorptive symptoms -which are believed to be associated with rapid rise in serum lithium levels -to occur at night while the patient is sleeping.

In one study, significantly less sclerotic glomeruli, atrophic tubules and interstitial fibrosis were observed in patients on a single daily dosage regimen, as compared to patients on a multiple daily dosage regimen.

Comparative Bioavailability

Two comparative bioavailability studies were performed using healthy human volunteers- one under fasting conditions, and one with food. The rate and extent of absorption of lithium carbonate was measured and compared following oral administration of two 300 mg capsules of either Apo-Lithium Carbonate or Carbolith. The results from measured data are summarized as follows:

Fasting Study: Summary Table of the Comparative Bioavailability Data Lithium (Dose: 600 mg) From Measured Data			
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means(%)**
	Apo-Lithium Carbonate	Carbolith®†	

UCT (mcg•hr/mL)	60.0 60.7 (15)	60.5 61.2(15)	99.2
UC1 (mcg•hr/mL)	64.8 65.6 (16)	65.0 65.9 (17)	99.6
Cmax (mcg/mL)	4.26 4.30 (13)	4.62 4.65 (13)	92.4
Tmax (hr)*			—
t112 (hr)*	2.05(41)	1.96 (53)	

* Arithmetic means (CV%).

**Based on the least squares estimate.

†Carbolith® (ICN Canada Ltd.) was purchased at a Canadian retail pharmacy.

Fed Study: Summary Table of the Comparative Bioavailability Data

I Lithium (Dose: 600 mg) From Measured Data

	Geometric Mean Arithmetic Mean (CV%)		
	Apo-Lithium Carbonate	Carbolith®t	Ratio of Geometric
UCT (mcg•hr/ml)	57.1 57.4 (11)	58.2 58.5 (10)	98.3
UC1 (mcg•hr/ml)	63.3 63.8 (13)	64.7 65.1 (12)	98.1
Cmax (mcg/ml)	3.76 3.79 (12)	3.90 3.93 (12)	96.6
Tmax (hr)*			—
t112 (hr)*	3.05 (25)	2.60 (32)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

†Carbolith® (ICN Canada Ltd.) was purchased at a Canadian retail pharmacy.

INDICATIONS:

In the lithium treatment of manic episodes of manic-depressive illness. Maintenance therapy has been found to be useful in preventing or diminishing the frequency of subsequent relapses in bipolar manic-depressive patients (with a history of mania). 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.

CONTRAINDICATIONS:

APO-LITHIUM CARBONATE (lithium carbonate) should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or 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 adjustments to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is necessary.

WARNINGS:

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.

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (See DOSAGE).

Impaired Renal Function:

Chronic lithium therapy is frequently associated with a decrease in renal concentrating capacity with development of thirst, polyuria, micturia, weight gain and altered kidney function tests, occasionally presenting as nephrogenic diabetes insipidus. Such patients should be carefully managed 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 reassessment of the risk-benefit of long-term lithium therapy.

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.

Pregnancy: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 child-bearing 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 foetus.

Lactation: 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.

Children: Since information regarding the safety and effectiveness of lithium in children under 12 years of age is not available, the use of lithium carbonate in such patients is not recommended at this time.

PRECAUTIONS:

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 control procedures required during treatment, as well as an explanation of the expected benefits and the most commonly experienced immediate and long-term side effects. In most cases, appropriate written material should be provided to supplement verbal information.

Out-patients and their families should be warned that the patient must discontinue therapy and contact the physician if clinical signs of lithium toxicity such as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

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

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium therapy; where hypothyroidism exists, careful monitoring of the 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.

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 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.

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.

DRUG INTERACTIONS:

Combined use of haloperidol and lithium*:* An encephalopathy resembling the malignant neuroleptic 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 concomitant administration of lithium and haloperidol has not been clearly established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity such as rigidity and/or hyperpyrexia and treatment discontinued promptly if such signs appear.

Combined use of phenothiazines and lithium: 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 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. Therefore, the clinician should be alert for altered response to either drug when used in combination and when either drug is withdrawn.
The action of neuromuscular blocking agents may be prolonged in patients receiving lithium. Therefore, 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.

Indomethacin has been reported to increase steady state plasma lithium levels by 30 to 59%. There is also evidence that other nonsteroidal anti-inflammatory agents may have a similar effect. When such combinations are used, increased frequency of monitoring plasma lithium levels is recommended.
There are reports that concurrent use of methyldopa or tetracycline may increase the risk of lithium toxicity.
Concurrent use of lithium and carbamazepine or phenytoin might result in an increased risk of CNS toxicity. The administration of aminophylline or theophylline to patients on lithium therapy may require increased lithium doses to maintain the psychotropic effect. 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.

ADVERSE REACTIONS:

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 rapid rise in serum lithium levels. They include nausea, abdominal pain, vomiting, diarrhea, vertigo, muscle weakness, sleepiness and a dazed feeling, and 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 elderly 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 gastrointestinal 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.

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 (fasciculations, twitching, clonic movements of whole limbs), ataxia choreoathetotic movements, hyperactive deep tendon reflexes.

CNS: blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma.
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, acne, chronic folliculitis, xerosis cutis, alopecia and exacerbation of psoriasis.

Autonomic Nervous System: blurred vision, dry mouth.

Thyroid Abnormalities: 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 PRECAUTIONS). Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes: diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

ECG Changes: reversible flattening, isoelectricity or inversion of T waves.

Miscellaneous: fatigue, lethargy, transient scotomata, dehydration, weight loss, tendency to sleep.

Miscellaneous reactions frequently unrelated to dosage include: transient EEG and ECG changes, leucocytosis, headache, diffuse non-toxic goiter with or without hypothyroidism, transient hyperglycemia, generalized pruritus with or without rash, cutaneous ulcers, albuminuria, worsening of organic brain syndrome, excessive weight gain, edematous swelling of ankles or wrists, and thirst or polyuria, sometimes resembling diabetes insipidus, and metallic taste.
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 starting treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

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

OVERDOSAGE:

Symptoms: Lithium toxicity is closely related to the concentration of lithium in the blood and is usually associated with serum concentrations in excess of 1.5 mEq or mmol/L. Early signs of toxicity which may occur at lower serum concentrations were described under Adverse Effects 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 reassessment and management. Signs and symptoms of lithium intoxication have already been described under Adverse Effects.

Treatment of Overdosage:
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 and supportive care.
Recommended treatment consists of gastric lavage, correction of fluid and electrolyte imbalance and 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.

DOSAGE AND ADMINISTRATION:

Dosage: Selection of patients and approach to lithium therapy: The results of lithium therapy depend largely on the nature and course of the illness itself, rather than on the symptoms. The selection of patients for long-term treatment requires a clearcut diagnosis of primary affective disorder, the condition for which the stabilizing effects of lithium have been found useful. The variables that have been more consistently associated with response to lithium therapy in patients with a primary affective disorder are: the good quality of remissions with good function and no significant symptomatology during the free intervals between previous episodes of illness; low frequency of episodes, typically 1 or 2 (and not more than 3 or 4) per year; and symptomatology during the acute episodes that meet strict criteria for a primary affective disorder (DSM-III; Research Diagnosis Criteria).
Screening for lithium candidates should include at least, a medical history and physical examination with emphasis on the CNS, urinary, cardiovascular, gastrointestinal and endocrine systems and the skin. It should also include routine 24 hour urine volume, serum

creatinine, record of weight, and 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.

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. Three 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 cooperation of patients and relatives is required throughout. Before deciding on the institution of long-term treatment, it is essential to establish that the patient has clearly responded to a course of stabilizing lithium therapy and that the risk of such therapy is acceptable. Maintaining a patient with a lithium nonresponsive condition on long-term therapy poses an unacceptable risk. A decision with regards to long-term therapy can be made during a time-limited trial of lithium therapy with frequent reassessment of outcome. The following are among the factors to be reassessed 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. Assessment of response to treatment is based strictly on firm evidence of relapse prevention during a reasonable trial period, but can be assisted by consideration of the predictors of response outlined above. Great pains should be taken to exclude false responders and false non-responders. It should also be borne in mind that non-responders are more susceptible to the adverse effects of lithium.

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 concentrations and clinical response. The dosage should be adjusted to obtain serum concentrations between 0.8 and 1.2 mEq or mmol/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 daily dosage for acute mania is 900 to 1800 mg (15 to 20 mg/kg), divided into 3 doses. In view of the large variability of renal lithium excretion between individuals, it is suggested that lithium treatment be started at a dose between 600 and 900 mg/day, reaching gradually a level of 1200 to 1800 mg in 3 divided doses. Depending on the patient's clinical condition, the initial dosage should be adjusted to produce the desired serum lithium concentration. The weight of the patient should also influence the choice of the initial dose.

Elderly Patients:

Lithim should be used cautiously and in reduced doses in the elderly patient, usually in the range of 600 to 1200 mg/day. Serum lithium concentrations should be monitored frequently and kept below 1.0 mEq/L or mmol/L.

Maintenance Therapy:

After the acute manic episode subsides, the dosage should be rapidly reduced to achieve serum concentrations between 0.6 and 1.0 mEq or mmol/L, since there is evidence at this time of a decreased tolerance to lithium. The average suggested dosage at this stage is 900 mg/day (approximately 25 mEq), divided into 3 doses, with a range usually between 500 and 1200 mg/day. If a satisfactory response to antimanic lithium is not obtained in 14 days, consider discontinuing lithium therapy. When the manic attack is controlled, maintain lithium administration during the expected duration of the manic phase, since early withdrawal might lead to relapse. It is essential to maintain clinical supervision of the patient and monitor lithium concentrations as required during treatment (see PRECAUTIONS).

Once patients are stabilized on a maintenance dose with a multiple dosing schedule, and once stable therapeutic blood levels are reached, the dosage schedule may be changed to a once daily dosage administration.

The total daily dose, when administered as a single daily dose, may be approximately 5 to 30% lower than when given in divided doses over the day.

It is essential to maintain clinical supervision of the patient and to monitor serum lithium levels both when using the divided daily dosage regimen and when transferring to the once daily administration dosage regimen.

In uncomplicated cases receiving maintenance therapy during remission, serum lithium levels should be monitored at least every two months.

Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1 to 1.4 mEq/L.

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

NOTE:

Blood samples for serum lithium determination should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e. 12 ± 1 hour after the previous dose of lithium). Total reliance must not be placed on serum levels alone. Adequate patient evaluation requires both clinical assessment and laboratory analysis.

Use in Children:

Lithium is not recommended for routine use in children under 12 years of age since information in this age group is not yet available.

PHARMACEUTICAL INFORMATION:

Drug Substance: Apo-Lithium Carbonate

Structural Formula: Li_2CO_3

Molecular Weight: 73.89

CHEMISTRY:

Description: Lithium is a monovalent cation which belongs to the group of alkali metals together with sodium, potassium and other elements with which is shares some of its properties. Lithium is extremely reactive. It is present in trace amounts in animal tissues, but its possible physiological role is not known.

Lithium carbonate is a white, odourless, amorphous or microcrystalline powder that melts at 618°. Lithium carbonate is slightly soluble in water and practically insoluble in alcohol. It dissolves, with effervescence, in dilute mineral acids. A saturated solution is alkaline to litmus. One g of lithium carbonate corresponds to 27 mmol of lithium; one 150 mg Apo-Lithium Carbonate capsule contains approximately 4.0 mmol, one 300 mg Apo-Lithium Carbonate capsule contains approximately 8.1 mmol of lithium.

Composition Capsules: Apo-Lithium Carbonate 150 mg and 300 mg capsules contain lithium carbonate. The capsule shells contain the non-medicinal ingredients gelatin, titanium dioxide, D&C yellow #10 (150 mg only), FD&C yellow #6 (300 mg only), FD&C red #40 and D&C red #28. The edible black printing ink on the capsule shell contains the non-medicinal ingredient black iron oxide.

Stability and Storage :

Store away from heat, direct light, at room temperature between 15 and 30 C. Do not store in humid place (bathroom). Keep in well closed container. Keep out of reach of children.

Special Instructions: Other medicines together with lithium carbonate should not be taken without advice from a physician. Lithium carbonate should be taken with food and swallowed in whole and should not be broken or chewed. It is important to consume sufficient fluid and a well-balanced sodium intake.

AVAILABILITY:

Ape-Lithium Carbonate 150 mg; each orange and white, size #4 capsule imprinted "APO 150" contains lithium carbonate 150 mg. Available in bottles of 100, 500 and 1000 capsules.

Ape-Lithium Carbonate 300 mg; each flesh coloured, size #2 capsule imprinted "APO 300" contains lithium carbonate 300 mg. Available in bottles of 100, 500 and 1000 capsules.

PHARMACOLOGY:

Lithium ions are rapidly absorbed from the Gl tract and plasma lithium peaks are reached 2-4 hours after lithium administration. The distribution of lithium in the body approximates that of total body water, but its passage across the blood-brain barrier is slow and at equilibration the CSF lithium level reaches only approximately half the plasma level.

Lithium is excreted mainly through the kidneys with less than 1% being eliminated with the feces. Lithium is filtered by the glomeruli and 4/5 of the filtered lithium are reabsorbed in the tubules, probably by the same mechanism responsible for sodium reabsorption. The renal clearance of lithium is proportional to its plasma concentration. About half a single dose of lithium is excreted in 24 hours.

A low salt intake resulting in low tubular concentration of sodium will increase lithium reabsorption and might result in retention or intoxication.

Renal lithium clearance is, under ordinary circumstances remarkably constant in the same individual but decreases with age and falls 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 must, therefore, be adjusted individually. In clinical reports, it has been noted that serum lithium may rise an average of 0.2 - 0.4 mmol/litre after intake of 300 mg and 0.3 - 0.6 mmol/litre after intake of 600 mg of lithium carbonate. It has been suggested that manic 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 seem to have an increased tolerance to lithium.

Lithium is inactive in most screening psychopharmacological tests but it produces 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 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.

EKG changes with lithium have been reported in both animals and man.

TOXICOLOGY:

The oral ED_{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. EKG 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; 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 tubule of dogs and in the proximal convoluted tubules of rats. The primary toxic effects in man appear to be on the central nervous system.

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

Reproductive Studies: 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 resorption, embryonal viability and weaning weights in rats, the number of implantation sites in rabbits, and the birth weights in monkeys, have been produced in lithium studies. Cleft palates occurred in the offspring of treated mice and rats, in the latter species together with ocular and auricular defects, with lithium doses producing blood levels similar to those obtained with therapeutic doses in man.

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

The retrospective studies congenital abnormalities were observed in 6% of infants born to mothers taking lithium carbonate during the first trimester of pregnancy. This incidence was considered to be no greater than that observed in the general population of infants.

Infants born to mothers who took lithium during pregnancy had a higher than expected ratio of cardiovascular anomalies (6%).

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