PRODUCT MONOGRAPH

PrEURO LITHIUM

Lithium Carbonate
Capsules, 150 and 300 mg

Antimanic Agent

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Control # 119104

NAME OF DRUG

EURO LITHIUM
(Lithium carbonate)

Capsules 150 and 300 mg

THERAPEUTIC CLASSIFICATION

Antimanic agent

ACTION and CLINICAL PHARMACOLOGY

Although lithium is useful for its antimanic effect and in preventing relapses in patients with a clear-cut diagnosis of bipolar affective disorder, it has very little, if any, direct effect on moods, normal or abnormal. Lithium alters sodium transport in nerve and muscle cells, affects a shift toward intraneuronal metabolism of catecholamines and has an inhibitory action on the intracellular formation of cyclic AMP. However, the specific biochemical mechanism of action of lithium in mania is still largely unknown.

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.

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

Pharmacokinetics:

Lithium ions are rapidly absorbed from the gastrointestinal (GI) tract following oral administration of **Euro Lithium** (lithium carbonate). Peak plasma lithium concentrations are reached 2-4 hours after **Euro 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 is excreted primarily in urine with less than 1% being eliminated with the feces. Lithium is filtered by the glomeruli and 4/5 (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. The half-life of elimination of lithium is approximately 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 in 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/L after intake of 300 mg and 0.3 -0.6 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 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.

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.

INDICATIONS

Euro Lithium (lithium carbonate) is indicated in the treatment of acute manic episodes in patients with manic-depressive disorders. Maintenance therapy has been found useful in preventing or diminishing the frequency of subsequent relapses in bipolar manic-depressive patients (with a strong history of mania).

CONTRAINDICATIONS

Euro Lithium (lithium carbonate) is contraindicated in patients with significant cardiovascular or renal disease. It is also contraindicated in patients with evidence of severe debilitation or dehydration, sodium depletion, brain damage, and in conditions requiring low sodium intake.

WARNINGS

Therapy with Euro Lithium (lithium carbonate) requires reaching plasma levels of lithium which are relatively close to the toxic level. Since lithium is excreted primarily by the kidney, adequate renal function and adequate salt and fluid intake (2500 to 3000 mL) are essential in order to avoid lithium accumulation and intoxication. Thus, a decision to initiate lithium therapy should be preceded by a thorough clinical examination and evaluation of each patient, including laboratory determinations, ECG, and a very careful assessment of renal function.

Means of obtaining accurate determination of serum lithium levels should be available, since frequent serum determinations are required specially during the initial period of treatment. Lithium toxicity is closely related to serum lithium levels and during treatment they should usually not exceed 1.5 mmol/L, if serious adverse reactions and lithium intoxication are to be avoided. This lithium level refers to a blood sample drawn before the patient has had his/her first lithium dose of the day, therefore, 9 - 12 hours after his/her last dose of drug. Serum lithium levels should usually be monitored three times weekly during the initial period of administration and periodically as required thereafter. If lithium levels exceed 1.5 - 2 mmol/L, the drug should be discontinued and, if appropriate, administration resumed at a lower level after 24 hours. Prodromal toxic signs such as fatigue, muscular weakness, incoordination, drowsiness, coarse tremors, diarrhea and vomiting, provide a sensitive warning of lithium intoxication.

In view of the limited dosage range of lithium compared to other psychotropic agents, particular care is required for the patient to receive exactly the prescribed number of **Euro Lithium**capsules.

Good kidney function and adequate salt and fluid intake are essential to maintain lithium excretion. When sodium intake is lowered, lithium excretion is reduced. Diminished intake or excessive loss of salt and fluids, as a result of vomiting, diarrhea, perspiration or use of diuretics will also increase lithium retention. Thus, lithium should not be given to patients on a salt-free diet and sodium depletion must be carefully avoided. Therefore, it is essential for the patient to maintain a normal diet including adequate salt and fluid intake during lithium therapy. Salt supplements and additional fluids may be required if excessive losses occur. **Euro Lithium** should generally not be given to patients receiving diuretics, since the risk of lithium toxicity is very high in such patients. If diuretics are used during lithium therapy the serum lithium concentration must be closely monitored.

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. Morphological 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 re-evaluation of treatment.

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 neurologic toxicity and treatment discontinued promptly if such signs appear (also see **PRECAUTIONS, Drug Interactions**). The possibility of similar adverse interactions with other antipsychotic medication exists (see **PRECAUTIONS, Drug Interactions).**

Outpatients and their families should be warned that patients must discontinue Euro Lithium (lithium carbonate) therapy and contact their physician immediately if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, fatigue or muscular weakness occur.

There is evidence of decreased tolerance to lithium once the acute manic episode breaks. Therefore, when the acute attack subsides, the dosage should be reduced rapidly in order to produce serum lithium levels no higher than between 0.6 and 1.2 mmol/L.

PRECAUTIONS

General

Periodic review and monitoring of kidney and cardiovascular function is advisable during therapy with lithium carbonate. Other laboratory tests should be performed as indicated by the patient's clinical condition. The appearance of signs of toxicity or a rise in the blood level of lithium after the dosage is stabilized should alert the physician to determine the reasons for lithium accumulation.

Patients with Special Diseases and Conditions

(i) Patients with Cardiovascular Disease

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

(ii) Thyroid Disorder

Since the formation of non-toxic goiters has been reported during lithium therapy, the thyroid gland should be examined before treatment and appropriate thyroid function tests performed. Non toxic goiters reported during prolonged lithium therapy have disappeared following discontinuation of the medication. Treatment with small doses of thyroxin or desiccated thyroid in patients who develop a diffuse non-toxic goiter may stop further growth or lead to shrinkage of the gland.

(iii) Concomitant Infection

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

Use in Pregnancy or in Women of Child Bearing Potential

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 fetus.

In various animal species lithium affects reproduction and has been noted to have teratogenic effects. (see **TOXICOLOGY** - Reproductive Studies). A group of spontaneous reports concerning 37 mothers who received lithium during pregnancy included two who gave birth to infants with congenital malformations. Data from lithium birth registries suggests that the drug may increase the incidence of cardiac and other anomalies, especially Ebstein's anomaly.

When possible, lithium should be withdrawn for at least the first trimester unless it is determined that this would seriously endanger the mother.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be appraised for the potential hazards to the fetus.

When lithium is used during pregnancy, serum lithium concentrations should be carefully monitored and dosage adjusted if necessary since renal clearance of the drug and distribution of the drug into erythrocytes may be increased during pregnancy. Pregnant women receiving lithium may have subtherapeutic serum lithium concentrations if dosage of the drug is not increased during pregnancy.

Immediately postpartum, renal clearance of lithium may decrease to pre-pregnancy levels; therefore, to decrease the risk of postpartum lithium intoxication, dosage of the drug should be reduced from 1 week before parturition.

Use in Nursing Mothers

Lithium is excreted in human milk (concentrations of 33-50% of those in the mother's serum). Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the opinion of the physician, the potential benefits to the mother outweighs possible hazards to the child.

Use in the Elderly

Geriatric patients appear to be more susceptible to adverse effects even when lithium levels are therapeutic.

Use in Children

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. 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.

Discontinuation of Therapy

The majority of patients do not experience withdrawal symptoms or rebound phenomenon upon cessation of long-term lithium therapy. In view of the occasional reports of sudden relapses occurring with abrupt discontinuation, gradual discontinuation is recommended unless abrupt withdrawal is necessary because of toxicity.

Drug Interactions

Diuretics or Angiotensin Converting Enzyme (ACE) Inhibitors

Caution should be exercised when lithium and diuretics or ACE inhibitors are used concomitantly because sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium plasma levels is recommended. (see also **WARNINGS**).

Haloperidol

It has been proposed that haloperidol and lithium could have a combined inhibitory effect on striatal adenylate cyclase. If haloperidol and lithium are used concomitantly, careful attention should be given to the dose of both agents as well as to early detection of neurotoxicity, particularly in the presence of one or more predisposing factors which include large doses of one or both drugs, the presence of acute mania, failure to discontinue drugs when adverse effects occur, pre-existing brain damage, a history of extrapyramidal symptoms with neuroleptic therapy alone, the concurrent use of anticholinergic

antiparkinsonian drugs, and the presence of other physiologic disturbances such as infection, fever, or dehydration. Also see **WARNINGS**.

Phenothiazines

Both pharmacokinetic interactions and clinical toxicity with the combined use of phenothiazines and lithium 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.

Non-Steroidal Anti-Inflammatory Drugs (NSAID)s

NSAIDs have been reported to increase significantly, steady state plasma lithium levels. In some cases lithium toxicity has resulted from such interactions. In a patient stabilized on lithium and NSAIDs, discontinuation of the NSAIDs may result in inadequate serum lithium concentrations. When such combinations are used, increased plasma lithium level monitoring is recommended.

Selective Serotonin Reuptake Inhibitors (SSRI) Drugs

Lithium may enhance the serotonergic effects of SSRI drugs. Co-administration of lithium with SSRI drugs may lead to a higher incidence of serotonin associated side effects and lithium toxicity.

Fluvoxamine: Several cases of adverse reactions including convulsions have been reported in patients receiving concomitant lithium and fluvoxamine.

Fluoxetine: There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported.

Sertraline: In placebo-controlled study in normal volunteers sertraline did not alter steady-state concentrations or renal clearance of lithium. However, there was a high incidence of apparently treatment-related side effects with the combination in this study, tremors being the most frequently observed. There is no clinical experience with lithium in sertraline treated patients.

Therefore, combined use of lithium and SSRI drugs should be carried out with caution. Lithium levels should be monitored when these drugs are administered concomitantly, so that appropriate adjustments to the lithium dose may be made if necessary.

Carbamazepine

Several cases of neurotoxicity (in the absence of toxic serum lithium concentrations) have been reported in patients receiving lithium and carbamazepine, but the combination has also been used to advantage in some manic patients. Patients should be monitored for evidence of lithium toxicity when carbamazepine is given concurrently. It is not yet established whether plasma lithium concentrations are useful in monitoring this interaction since the carbamazepine might increase the effect of lithium without increasing plasma lithium concentrations.

Neuromuscular Blocking Agents

In patients receiving chronic lithium therapy, the action of neuromuscular blocking agents (eg succinylcholine, pancuronium) may be prolonged.

Theophylline

Theophylline enhances the renal clearance of lithium in most patients, thus tending to reduce serum lithium concentrations. When initiating lithium therapy in a patient on chronic theophylline, lithium dosage requirements may be higher than anticipated. When initiating theophylline therapy in a patient on chronic lithium, there may be reduced lithium response. Discontinuation of theophylline in a patient on chronic lithium may result in excessive lithium response. Monitoring of serum lithium concentration is recommended.

Calcium Channel Blockers (CCBs)

The addition of verapamil or diltiazem to patients stabilized on lithium therapy may result in neurotoxicity. The CCB effects may be additive to that of lithium on transmitter secretion in the nervous system. The use of CCBs in the treatment of patients with bipolar disorders receiving lithium should be commenced carefully with observation for neurotoxic effects. The therapeutic range of lithium may need to be toward the lower end when a CCB is co-administered.

Propranolol

Limited clinical data suggests that propranolol may increase lithium serum concentrations, and its coadministration with lithium may produce bradycardia. Pending further data, patients maintained on lithium should be monitored for changed lithium serum concentrations or exaggerated beta-blocker effects.

Tricyclic Antidepressants

Both lithium and tricyclic antidepressants lower the seizure threshold. An additive effect is possible.

Potassium Iodide

The hypothyroidic and goitrogenic effects of lithium carbonate and potassium iodide (and possibly other iodides) may be additive if the two drugs are used concurrently.

Diazepam

An isolated case has been reported of serious hypothermia during concurrent treatment with lithium and diazepam. Since hypothermia is potentially fatal if it occurs and its general incidence is not known, it would be prudent to watch for this interaction during concurrent treatment.

Sodium Bicarbonate

Patients on combined sodium bicarbonate and lithium therapy should be monitored for decreased lithium effects. Lithium blood levels may be helpful in assessing this interaction.

Sodium Chloride

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

Urea

Limited clinical experience indicates that urea may enhance the renal excretion of lithium resulting in reduced lithium serum concentrations.

Other

Isolated cases of lithium toxicity have been reported to be induced by concomitant administration of mazindol, methyldopa and phenytoin.

ADVERSE REACTIONS

Mild side effects may be encountered with **Euro Lithium** (lithium carbonate) even when serum lithium values remain below 1 mmol/L. The most frequent side effects are the initial postabsorptive symptoms, believed to be associated with a rapid rise in serum lithium levels. They include, gastrointestinal discomfort, nausea, vertigo, muscle weakness and a dazed feeling, and frequently disappear after stabilization of therapy. The more common and persistent adverse reactions are: fine tremor of the hands, and, at times, fatigue, thirst, and polyuria. These do not necessarily require reduction of dosage.

Mild to moderate toxic reactions may occur at lithium levels from 1.5 - 2 mmol/L, and moderate to severe reactions at levels above 2 mmol/L.

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 lower 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 GI 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 adverse reactions have been reported and are usually related to serum lithium levels:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, abdominal pain, and weight loss.

Neuromuscular: General muscle weakness, ataxia, tremor, muscle hyperirritability, (fasciculation, twitching, especially of facial muscles and clonic movements of the limbs), choreoathetotic movement, and hyperactive deep tendon reflexes.

Neurological: 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.

Central and Peripheral Nervous System: Urinary and fecal incontinence, slurred speech, blackout spells, seizures, cranial nerve involvement, psychomotor retardation, somnolence, toxic confusional states, restlessness, stupor, and coma.

Cardiovascular: Arrhythmia, hypotension, peripheral circulatory failure, cardiac collapse, and peripheral edema.

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

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

Autonomic Nervous System: Blurred vision, dry mouth.

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.

Genitourinary: Albuminuria, oliguria, polyuria, and glycosuria.

Dermatologic: drying and thinning of hair, anesthesia of skin, chronic folliculitis, xerosis cutis, alopecia, exacerbation of psoriasis, rash, and pruritus.

Allergy: Allergic vasculitis.

Metabolic and Nutritional Disorders: Thirst, hyperglycemia, and dehydration.

Hematopoietic and Lymphatic: Anemia, leukopenia, leukocytosis.

General: General fatigue, leg ulcers, metallic taste, and slight elevation of plasma magnesium.

Miscellaneous Reactions Unrelated to Dosage Are: Transient electroencephalographic and electrographic changes, hyperthyroidism, worsening of organic brain syndromes, excessive weight gain, edematous swelling of ankles or wrists. A single report has been recieved of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment of 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 centers on kidney function, the thyroid, parathyroid, the bones and skin.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Lithium toxicity is closely related to the concentration of lithium in the blood and is usually associated with serum levels in excess of 2 mmol/L. Early signs of toxicity which may occur at lower serum levels were described under **ADVERSE REACTIONS** and usually respond to reduction of dosage. Lithium intoxication has been preceded by the appearance or aggravation of the following symptoms: sluggishness, drowsiness, lethargy, coarse tremors or muscle twitching, 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 REACTIONS**.

In eight cases of lithium poisoning described by Schou, the patients frequently developed muscle rigidity with hyperactive deep reflexes, generalized muscle tremors or fasciculations, attacks of hyperextension of the limbs with gasping and wide opening of the eyes, and sometimes epileptic seizures and various neurological dysfunction. There was progressive impairment of consciousness and in some patients coma. EEG changes in some patients consisted of decrease of alpha activity and increase of theta and delta activity, the latter at times paroxysmal with maximal activity frontally. Periods of beta activity with sharp waves were also observed. The kidney function was probably impaired in several patients. Three of these patients died, all of pulmonary complications.

Treatment

No specific antidote for lithium poisoning is known. The treatment of lithium poisoning is symptomatic. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the organism. Treatment of lithium poisoning is 1) lavage, 2) correction of fluid and electrolyte imbalance, and 3) regulation of kidney function. Sodium depletion in particular must be corrected. However, adminstration of large amounts of sodium in the absence of depletion of this electrolyte has not been very successful in many as a means of speeding lithium excretion. Lithium excretion may be facilitated by the judicious use of intravenous urea, sodium bicarbonate, acetazolamide or aminophylline. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient or in the presence of impaired renal function. Infection prophylaxis, regular chest X-rays and preservation of adequate respiration are essential.

DOSAGE AND ADMINISTRATION

Since lithium acts without the production of "sedation", some prefer it to neuroleptics or use these to supplement lithium therapy and obtain rapid control of overt manic behaviour. Lithium also has a useful indication in those cases that fail to respond to neuroleptics.
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 Diagnostic 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, an ECG, possibly electrolytes and TSH, and for long-term treatment, creatinine clearance and a urine concentration test. Other examinations and tests should be used when indicated. Monitoring lithium treatment should include, for each visit, mental status, physical examination, weight, 12 hour serum lithium and a check for lithium side effects and compliance. It should also include serum creatinine every 2 months, plasma thyroid hormone and TSH every 6 to 12 months, particularly in female patients, and attention to renal and thyroid function should be maintained throughout, with tests used for baseline screening repeated as required.

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

In properly screened adult patients, the suggested initial daily dosage for acute mania is 1800 mg (approximately 50 mmol), divided into three 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 a level of 1200 to 1800 mg in divided doses on the second day. Depending on the patient's clinical condition, the initial dosage should be adjusted to produce the desired serum lithium level.

The weight of the patient should also influence the choice of the initial dose.

Euro Lithium should be used cautiously and in reduced doses in the elderly patient, usually in the range of 600 to 1200 mg/day. Serum lithium levels should be monitored frequently and kept below 1.5 mmol/L.

Long Term Control

After the acute manic episode subsides, usually within a week, the dosage of **Euro Lithium** should be rapidly reduced to achieve serum levels between 0.6 and 1.2 mmol/L (with the level kept below 1.5 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 mmol), divided into three doses, with a range usually between 600 and 1200 mg/day. If a satisfactory response is not obtained in 14 days, lithium therapy should be discontinued. When the manic attack is controlled, lithium administration should be maintained 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 levels as required during treatment. (See **WARNINGS** and **PRECAUTIONS**)

Lithium may be used concomitantly with neuroleptic drugs. (See **WARNINGS, PRECAUTIONS, Drug Interactions)**

Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every 2 months.

Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0 to 1.4 mmol/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 determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e. 8-12 hours after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

PHARMACEUTICAL INFORMATION

i. **DRUG SUBSTANCE**

Proper Name:	Lithium Carbonate
Molecular Formula:	Li_2CO_3
Molecular Weight:	73.89
Description:	Lithium is a monovalent cation which belongs to the group of alkali metals together with sodium, potassium and other elements with which it shares some of its properties.
	Lithium carbonate is a white, odourless, amorphous or microcrystalline powder. One gm of lithium carbonate corresponds to 27 mmol of lithium and one 300 mg **EuroLithium** (lithium carbonate) Capsule contains approximately 8.1 mmol of lithium.

ii. **COMPOSITION**

Euro Lithium capsules (hard gelatin capsules) contain 150 and 300 mg of lithium carbonate. There are no non-medicinal ingredients used.

AVAILABILITY

Dosage Forms

Euro Lithium(lithium carbonate) is available as capsules containing 150 and 300 mg of lithium carbonate.

Euro Lithium capsules contain pure lithium carbonate with no non-medicinal ingredients. The 300 mg green and ivory #1 capsules are available in opaque plastic bottles (HDPE) of 1000 capsules. The 150 mg ivory #3 capsules are available in opaque plastic bottles of 100 and 1000 capsules.

STORAGE

Store at 15-30°C.

TOXICOLOGY

Acute Toxicity (Mice and Rats)

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

Subacute Toxicity

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

The principal toxic effects of lithium are on the kidney with lesions in the distal convoluted 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.

Long Term Toxicity

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

Reproduction

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.

SELECTED BIBLIOGRAPHY

1. Amdisen, A. Serum lithium determinations for clinical use. Scand J Clin Lab Invest 1967;20:104-8.
2. Amdisen A, Schou M. Biochemistry of depression. Lancet 1967;I:501-11.
3. Angst J, Weis P, Grof P, Baastrup PC, Schou M. Lithium prophylaxis in recurrent affective disorders. Br J Psychiatry 1970;116:599.
4. Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. Lancet 1970;II:326-30.
5. Baastrup PC, Schou M. Lithium as a prophylactic agent against recurrent depressions and manicdepressive
psychosis. Arch Gen Psychiatry 1967;16:162-72.
6. Blackwell B. Lithium. Lancet 1970;II:875.
7. Blackwell B, Shepherd M. Prophylactic lithium: another therapeutic myth? Lancet 1968;I:968-71.
8. Bowman JA. The application of resonance monochromators to the determination of lithium in blood serum by atomic absorption spectrophotometry. Anal Chim 1967;Acta 37:465-71.
9. Bunney W, Goodwin F, Davis J, Fawcett J. A behavioral-biochemical study of lithium treatment. Am J Psychiatry 1968;125:499-511.
10. Cade JF. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;2:349-52.
11. Carroll BJ, Steven L, Pope RA, Davis B. Sodium transfer from plasma to CSF in severe depression. Arch Gen Psychiatry 1969;21:77-81.
12. Coats DA, Trautner EM, Gershon S. The treatment of lithium poisoning. Aust Ann Med 1957;6:11-15.
13. Colburn R, Goodwin F, Murphy D, Bunney W, Davis J. Effect of lithium treatment on the uptake of norepinephrine by synaptosomes. Nature 1967;215:1395-7.
14. Coppen A. Mineral metabolism in affective disorders. Br J Psychiatry 1965;III:1133-42.
15. Coppen A, Shaw DM, Malleson A, Costain R. Mineral metabolism in mania. Br Med J 1966;1:71-5.
16. Coppen A, Malleson A, Shaw DM. Effects of lithium carbonate on electrolyte distribution in man. Lancet 1965;I:682-3.

17. Fann WE, Asher H, Luton F. Use of lithium in mania. Dis Nerv Syst 1969;30:605-10.
18. Fieve RR, Platman S. Follow-up studies of lithium and thyroid function in manic-depressive illness. Am J Psychiatry 1969;125:1443-5.
19. Fieve RR, Platman S. Lithium and thyroid function in manic-depressive psychosis. Am J Psychiatry 1968;125:527-30.
20. Fieve RR, Platman S, Plutchik R. The use of lithium in affective disorders: I. acute endogenous depression. Am J Psychiatry 1968;125:487-91.
21. Gershon S. Use of lithium salts in psychiatric disorders. Dis Nerv Syst 1968;29:51-5.
22. Gershon S, Yuwiler A. Lithium ion: a specific psychopharmacological approach to the treatment of mania. J Neuropsychiatry 1960;1:229-41.
23. Goodwin F, Murphy D, Bunney W. Lithium carbonate in depression and mania. Arch Gen Psychiatry 1969;21:486-96.
24. Goodwin J, Katz R, Kopin I. Effect of bromide on evoked release of monoamines from brain slices and intact atria. Nature 1969;221: 556-7.
25. Guistino P. Il citrato di litio nel trattamento degli strati di eccitazione psicotica. Riv Psychiat 1953;79:307-11.
26. Hartigen CP. The use of lithium salts in affective disorders. Br J Psychiatry 1963;109:810-14.
27. Hullin RP, McDonald R, Dransfield GA. Metabolic balance studies on the effect of lithium salts in manic-depressive psychosis. Fourth World Congr Psychiatry September 1966.
28. Johnson G, Gershon S, Hekimian L. Controlled evaluation of lithium and chlorpromazine in the treatment of manic state: an interim report. Compr Psychiatry 1968;9:563-73.
29. Kingstone E. The lithium treatment of hypomanic and manic states. Compr Psychiatry 1960;1:317-20.
30. Klein E, Lavie P, Meiraz R, Sadeh A, Lenox RH. Increased motor activity and recurrent manic episodes: predictors of rapid relapse in remitted bipolar disorder patients after lithium discontinuation. Biol Psychiatry 1992;31:279-84.
31. Little BR, Platman SR, Fieve RR. The measurement of lithium in biologic samples by atomic absorption spectrophotometry. Clin Chem 1968;14:1211-15.
32. Maggs R. Treatment of manic illness with lithium carbonate. Br J Psychiatry 1963;109:56-65.
33. Nassr D. Observations on the use of lithium carbonate in psychiatry. In J Neuropsychiatry

1966;2:160-5.
34. Nielsen J. Magnesium-lithium studies: 1. serum and erythrocyte magnesium in patients with manic states during lithium treatment. Acta Psychiatr Scand 1964;40:190-6.
35. Nilson A, Axelsson R. Psychopathology during long-term lithium treatment of patients with major affective disorders. Acta Psychiatr Scand 1989;80:375-88.
36. Noack C, Trautner E. The lithium treatment of maniacal psychosis. Med J Aust 1951;2:219-22.
37. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991;159:123-9.
38. Olafsson O. Lithium medferd vid psychosis manio-depressiva. Laeknabladid 1965;50:51-5.

39. Rice D. The use of lithium salts in the treatment of manic states. J Ment Sci 1956;102:604-11.
40. Page C, Benaim S, Lappin F. A long-term retrospective follow-up study of patients treated with prophylactic lithium carbonate. Br J Psychiatry 1987;150:175-9.
41. Roxburgh PA. The present status of lithium therapy in manic depressive psychosis. Can Psychiatr Assoc J 1970;15:201-4.
42. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509-22.
43. Schanberg SM, Schildkraut JJ, Kopin IJ. The effects of lithium ion on H-norepinephrine metabolism in brain. Biochem Pharmacol 1967;16:393-9.
44. Schlagenhauf G, Tupin JP, White R. The use of lithium carbonate in the treatment of manic psychosis. Am J Psychiatry 1966;123:201-6.
45. Schou M. Special review: lithium in psychiatric therapy and prophylaxis. J Psychiatr Res 1968;6:67-95.
46. Schou M. Lithium: elimination rate, dosage, control poisoning, goiter, mode of action. Acta Psychiat Scand 1969;207:49-53.
47. Schou M, Amdisen A, Trap-Jensen J. Lithium poisoning. Am J Psychiatry 1968;125:520-7.
48. Schou M, Baastrup P, Grof P, Weis R, Angst J. Pharmacological and clinical problems of lithium prophylaxis. Br J Psychiatry (in press).
49. Schou M, Juel-Nielsen N, Stromgren E, Voldby H. The treatment of manic psychoses by the administration of lithium salts. J Neurol Neurosurg Psychiatry 1954;17:250-60.
50. Stancer H. A longitudinal investigation of lithium as a prophylactic agent for recurrent depression. Can Psychiatr Assoc J 1970;15:29.
51. Suppes R, Baldessarini RJ, Gianni LF, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry December 1991;48:1082-8.
52. Szabo KT. Teratogenic effect of lithium carbonate in the foetal mouse. Nature 1970;225:73-5.
53. Teulie M, Follin, Begoin. Étude de l'action des sels de lithium dans états d'excitation psychomotrice. Encéphale 1955;44:266-85.
54. Thomsen K. Renal lithium elimination in man and active treatment of lithium poisoning. Acta Psychiatry Scand 1969;Suppl 207:83-4.
55. Trautner EM, Morris R, Noack CH, Gershon S. The excretion and retention of ingested lithium and its effects on the ionic balance of man. Med J Aust 1955;42:280-91.
56. Tupin J, Schlagenhauf G, Creson D. Lithium effects on electrolyte excretion. Am J Psychiatry 1968;125:536-42.
57. Vestergaard P, Aagaard J. Five-year mortality in lithium-treated manic-depressive patients. J Affective Disord 1991;21:33-8.