Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CAMCOLIT 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg Lithium Carbonate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White film coated tablet
The tablets are engraved "CAMCOLIT-S" around one face and having a scoreline on the reverse.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment and prophylaxis of mania, bipolar affective disorders illness and recurrent depression, and the treatment of aggressive or self mutilating behaviour.

4.2 Posology and method of administration

For oral administration.

CAMCOLIT 400mg film coated tablets are usually administered according to a twice daily regimen. When lithium levels have stabilised, a once daily regimen may be preferred.

4.2.1 Dosage

Lithium carbonate has a narrow therapeutic window. The dose required for treatment must be titrated and adjusted on the basis of regular monitoring of the serum concentration of lithium (See Section 4.4.1). Lithium therapy should not be initiated unless adequate facilities for routine monitoring of plasma concentrations are available.

On initiation of treatment, plasma therapy concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter.
Additional measurements should be made if signs of lithium toxicity occur, on dosage alteration, development of significant intercurrent disease, signs of manic depressions or depressive relapse and if significant change in sodium or fluid intake occurs. More frequent monitoring is required if patients are receiving any drug treatment that affects renal clearance of lithium e.g. diuretics and NSAID (See section 4.4 and section 4.5). As bioavailability may vary between formulations, should a change of preparations be made, blood levels should be monitored weekly until restabilisation is achieved.

Toxic symptoms are usually associated with lithium concentrations exceeding 1.5 mmol/l. Levels of more than 1.5 mmol/l must be avoided. In the event of toxicity, lithium should be withdrawn immediately.

Withdrawal
If lithium is to be discontinued for other reasons, particularly in cases of high doses, the dose should be reduced gradually over a suitable period of time, e.g. 2 weeks, to prevent the risk of relapse.

Acute mania:

Adults: Treatment should be initiated in hospital where regular monitoring of plasma lithium levels can be conducted. The dosage of Camcolit should be adjusted to produce a plasma lithium level between 0.6 and 1.0 mmol/l 12 hours after the last dose. The required plasma lithium level may be achieved in one of two ways but, whichever is adopted, regular estimations must be carried out to ensure maintenance of levels within the therapeutic range. For consistent results it is essential that the blood samples for plasma lithium estimations are taken 12 hours after the last dose of lithium.

1. 1,000-1,500 mg of lithium carbonate are administered daily for the first five days. A blood sample for plasma lithium estimation is taken 12 hours after the last dose on the fifth day, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the therapeutic range. Subsequently, regular plasma lithium estimations must be carried out and, where necessary, the dosage of Camcolit adjusted accordingly. The precise initial dose of lithium should be decided in the light of the age and weight of the patient; young patients often require a dose higher than average and older patients a lower dose.

2. A lithium clearance test is carried out and the initial dosage calculated from the results. Even when the initial dosage is calculated in this way, it is still desirable that plasma lithium levels should be determined at weekly intervals during the first three weeks of treatment, and any necessary adjustments to dosage made as a result of the levels actually obtained.

Most of the above applies in the treatment of hypomania as well as mania, but the patient (if not too ill) can be started on treatment as an outpatient provided that facilities for regular plasma lithium monitoring are available, and assays are initiated within one week.

Prophylaxis of recurrent affective disorders*:*
Adults: (Including unipolar mania & unipolar depressions and bipolar manic-depressive illness): A low dose of 300-400 mg of lithium carbonate can be administered daily for the first seven days. A blood sample for plasma lithium estimation is then taken 12 hours after the last dose, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the range of 0.4-0.8 mmol/l.

Aggressive and self mutilating behaviour
Adults: The dosage is at the lower end of the range for the treatment for manic depressive illness.

4.2.2 Special populations

Elderly:

Start treatment with a low dose.

Elderly patients often require a lower lithium dosage to achieve therapeutic serum levels. As for prophylaxis above, but 12 hour lithium levels should be kept in the range of 0.4-0.7 mmol/l as toxic symptoms are likely with plasma concentrations above 1.0 mmol/l. Toxic symptoms are more likely at lower concentrations than in the general population.

Children:

Not recommended.

4.3 Contraindications

- a history of hypersensitivity to lithium or any of the excipients listed in section 6.1.
- severely impaired renal function
- untreated or untreatable hypothyroidism.
- cardiac disease associated with rhythm disorder.
- brugada syndrome or family history of Brugada syndrome (see section 4.4)
- low body sodium levels for example dehydrated patients, those on low sodium diets, or those with Addison's disease
- breast feeding.

4.4 Special warnings and precautions for use

Lithium carbonate has a narrow therapeutic window. The dose required for treatment must be titrated and adjusted on the basis of regular monitoring of serum concentration of lithium. Lithium therapy should not be initiated unless adequate facilities for routine monitoring of plasma concentrations are available.

Elderly patients are particularly liable to lithium toxicity. Use with care as lithium excretion may also be reduced. They may also exhibit adverse reactions at serum levels ordinarily tolerated by younger patients (see section 4.2).

Before beginning a lithium treatment:

- It is important to ensure that renal function is evaluated (see sections 4.3 and 4.4.2).
- Thyroid function should be evaluated. Patients should be euthyroid before initiation of lithium therapy.
- Cardiac function should be assessed especially in patients with cardiovascular disease.

Renal, cardiac and thyroid functions should be re-assessed periodically.

Risk of convulsions
The risk of convulsions may be increased when lithium is co-administered with dmgs that lower the epileptic threshold, or in epileptic patients (see sections 4.5 and 4.8).

Benign intracranial hypertension
There have been case reports of benign intracranial hypertension (see section 4.8). Patients should be warned to report persistent headache and/or visual disturbances.

QT prolongation
As a precautionary measure, lithium should be avoided in patients with congenital long QT syndrome, and in patients concomitantly treated with drugs that are known to prolong the QT interval (see sections 4.5 and 4.8). Caution should be exercised in patients with risk factors for QT interval prolongation (which include cardiac disease, bradycardia, thyroid disease, hypokalaemia, hypomagnesaemia, hypocalcaemia, female sex and advanced age.

Brugada syndrome
Lithium may unmask or aggravate Brugada syndrome, a hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Lithium should not be administered to patients with Bmgada syndrome or a family history of Brugada syndrome (see section 4.3) Caution is advised in patients with a family history of cardiac arrest or sudden death.

Bariatric surgery
A lower maintenance dosage of Lithium may be required for patients, who have undergone a bariatric surgery because of decreased glomerular filtration following marked weight loss. Also, drug levels should be monitored closely in connection with bariatric surgery due to the risk of lithium toxicity.

Concomitant administration of antipsychotics
Concomitant administration of antipsychotics should be avoided.

4.4.1 Monitoring of blood lithium levels

Serum concentration of lithium should be measured on a sample taken just prior to the time when a dose of lithium is due to be taken (i.e. at trough level 12 hours following the last dose).

Toxic effects may be expected at serum-lithium concentrations of approximately 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously. Serum concentration of lithium should be measured every 5 to 7 days from initiation until stabilisation is achieved and at regular intervals for the duration of treatment.

Serum lithium concentrations should be monitored more frequently (revert to weekly monitoring) in the following circumstances:

- dosage alteration or change oflithium formulation (bioavailability may differ)
- significant intercurrent disease
- intercurrent infection
- significant change in sodium intake
- significant change in fluid intake
- treatment with drugs altering renal clearance of lithium
- treatment with drugs likely to upset electrolyte balance.

Patients should also be warned to report if polyuria or polydipsia develops (see section 4.4.2). Episodes of nausea and vomiting or other conditions leading to salt/water depletion (including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored.

4.4.2 Renal impairment

Lithium excretion is reduced in the presence of renal impairment. This increases the risk of toxicity. Lithium is contraindicated in patients with severe renal impairment (see section 4.3). If patients with mild or moderate renal impairment are being treated with lithium, serum lithium levels should be closely monitored.

Renal function should be monitored in patients with renal impairment, and in patients with polyuria and polydipsia.

4.4.3 Warnings to be given to patients about signs and symptoms of toxicity

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Section 4.9 for symptoms of intoxication) and advice given for the need for urgency in seeking medical assistance if these symptoms appear.

Renal tumours: cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years (see Section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions may occur as a result of increased or decreased lithium levels, or through other mechanisms, the most important being neurotoxicity which may occur at therapeutic levels when other drugs which act centrally on the CNS are taken concurrently.

Interactions which increase lithium concentrations:

Co-administration of the following drugs with lithium may lead to increased lithium concentrations and a risk of toxicity:

- any drug which may cause renal impairment has the potential to cause lithium levels to rise, thereby causing toxicity. If the use of the drug is unavoidable, carefully monitor lithium blood level and adapt dosage as necessary.
- antibiotics (metronidazole, tetracyclines, co-trimoxazole, trimethoprim), N.B. Toxic symptoms may also occur at low or normal levels when used in conjunction with co-trimoxazole or trimethoprim. Lithium toxicity has been reported on isolated occasions in patients receiving spectinomycin.
- non-steroidal anti-inflammatory drugs (including selective cyclo-oxygenase (COX) II inhibitors; monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued.
- drugs affecting the renin angiotensin system (ACE inhibitors, Angiotensin II receptor antagonists)
- diuretics (including herbal preparations). In addition to the effects noted above, thiazide diuretics show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication. Loop diuretics (e.g. furosemide, bumetanide and etacrynic acid) seem less likely to cause lithium retention, although caution is warranted.
- other drugs affecting electrolyte balance, e.g. steroids, may alter lithium excretion and should therefore be avoided.

Interactions which decrease serum lithium concentrations:

Co-administration of the following drugs with lithium may lead to decreased lithium concentrations and a risk of loss of efficacy:

- xanthine derivatives (e.g. theophylline, caffeine)
- products containing large quantities of sodium e.g. sodium bicarbonate
- carbonic anhydrase inhibitors.
- urea
- empagliflozin
- dapagliflozin

Interactions which may not be associated with increased or reduced lithium levels:

Concomitant use of the following drugs may precipitate symptoms of toxicity when the lithium level is within normal range:

- antipsychotic drugs such as haloperidol, thioridazine, fluphenazine, chlorpromazine and clozapine may lead in rare cases to neurotoxicity with symptoms such as confusion, disorientation, lethargy, tremor, extra-pyramidal symptoms and myoclonus. Increased lithium levels were present in some of the reported cases. Co administration of antipsychotics and lithium may increase the risk of Neuroleptic Malignant Syndrome, which may be fatal. Discontinuation of both drugs is recommended at the first signs of neurotoxicity.
- carbamazepine
- phenytoin
- methyldopa
- clonazepam
- tricyclic and tetracyclic antidepressants
- calcium channel blockers. These drugs may cause neurotoxic reactions at therapeutic levels
- neuromuscular blocking agents. Lithium may cause neurotoxic reactions at therapeutic lithium levels.

Selective serotonin re-uptake inhibitors (SSRIs): Concurrent use with lithium may precipitate a serotonergic syndrome.

Non-steroidal anti-inflammatory drugs including COX II inhibitors: monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued.

Triptans: lithium toxicity reported suggestive of serotonin syndrome.

Neruromuscular blockers: Lithium may prolong the effects of neuromuscular blocking agents.

Drugs which lower seizure threshold

Caution is advised if lithium is co-administered with drugs that lower the epileptic threshold (see section 4.4). e.g. antidepressants, antipsychotics, anaesthetics and theophylline.

Drugs which prolong the QT interval:

Lithium can cause an increase in the QTc interval, particularly at higher blood levels. Therefore concurrent use of drugs which have a risk of prolonging the QTc interval should be avoided (see section 4.4), and consideration be made of other potential risk factors such as increasing age, female sex, congenital long QT syndrome, cardiac and thyroid disease and the following metabolic disturbances: hypocalcaemia, hypokalaemia, hypomagnesaemia.

The following products have a high risk of causing QT prolongation and torsade de pointes:

- class Ia antiarrhythmics (ajmaline, cibenzoline, disopyramide, hydroquinidine procainamide, quinidine),
- class III antiarrhythmics (amiodarone, azimilide, dofetilidem, ibutide sotalol),
- antipsychotics (amisulpride; haloperidol, droperidol, mesoridazine, pimozide, sertindole, thioridazine and clozaril)
- antibiotics: (intravenous erythromycin, sparfloxacin)
- serotonin antagonists (ketanserin, dolasetron mesylate)
- antihistamines (astemizole, terfenadine)
- antimalarials (artemisinin derivatives, mefloquine, halofantrine)
- other: arsenic trioxide, cisapride and ranolazine

ECG should be performed after initiation of treatment and at any point where the patient becomes symptomatic or when there are changes in disease or treatment which may increase the risk of interaction or arrhythmia.

Non Drug Interactions:

- low sodium diet. Rapid reduction of sodium intake may cause raised lithium levels.
- intercurrent illness may cause lithium toxicity.

4.6 Fertility, pregnancy and lactation

Lithium therapy should not be used during pregnancy, especially during the first trimester unless considered essential. There is epidemiological evidence that it may be harmful to the foetus in human pregnancy. Lithium crosses the placental barrier.

In animal studies lithium has been reported to interfere with fertility, gestation and foetal development. An increase in cardiac and other abnormalities, especially Ebstein anomaly, are reported. Therefore, a pre-natal diagnosis such as ultrasound and electrocardiogram examination is strongly recommended. In certain cases were a severe risk to the patient could exist if treatment were stopped, lithium has been continued during pregnancy.

If it is considered essential to maintain lithium treatment during pregnancy, serum lithium levels should be closely monitored and measured frequently since renal function changes gradually during pregnancy and suddenly at parturition. Dosage adjustments are required. It is recommended that lithium be discontinued shortly before delivery and reinitiated a few days post-partum.

Neonates may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Neonates born with low serum concentrations may have a flaccid appearance that returns to normal without any treatment.

4.6.2 Women of child-bearing potential

It is advisable that women treated with lithium should adopt adequate contraceptive methods. In case of a planned pregnancy, it is strongly recommended to discontinue lithium therapy.

4.6.3 Lactation

Since adequate human data on use during lactation and adequate human reproduction studies are not available, and as lithium is secreted in breast milk, bottle feeding is recommended (see section 4.3 Contra-indications).

4.7 Effects on ability to drive and use machines

As lithium may cause disturbances of the CNS, patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable effects

Side effects are usually related to serum lithium concentrations and are less common in patients with plasma lithium concentrations below 1.0 mmol/l.

Initial therapy: fine tremor of the hands, polyuria and thirst may occur.

Blood and lymphatic system disorders: leucocytosis.

Immune system disorders: increase in antinuclear antibody.

Endocrine disorders: disturbances of thyroid function including (euthyroid) goitre, hypothyroidism and hyperthyroidism, hyperparathyroidism, parathyroid adenoma.

Metabolism and nutrition disorders: hypercalcaemia, hypermagnesaemia, hyperglycaemia, anorexia, weight gain.

Psychiatric disorders: Delirium.

Nervous system disorders: coma, pseudotumor cerebri, syndrome of irreversible lithium effectuated neurotoxicity (SILENT), encephalopathy, stupor, seizures, neuroleptic malignant syndrome, myasthenia gravis, serotonin syndrome, Parkinsonism, extrapyramidal symptoms, ataxia, dizziness, memory impairment, mild cognitive impairment, giddiness, nystagmus, slurred speech, vertigo, hyperactive deep tendon reflexes, dazed feeling, fine hand tremors.

Eye disorders: scotomata and blurred vision.

Cardiac disorders: cardiac arrest, arrhythmias including ventricular fibrillation, ventricular tachycardia, ventricular arrhythmias, Torsade de pointes, QT interval prolongation, arrhythmia, bradycardia, cardiomyopathy, sinus node dysfunction, ECG changes.

Vascular disorders: peripheral circulatory collapse, hypotension.

Gastrointestinal disorders: gastritis, nausea, diarrhoea, vomiting, dry mouth, excessive salivation. Lithium salts have been implicated in dysgeusia.

Skin and subcutaneous tissue disorders: allergic rash, exacerbation of psoriasis, acneiform eruptions, alopecia, acne, papular skin disorder, folliculitis, pruritus, rash.

Frequency unknown: Lichenoid drug reaction.

Musculoskeletal and connective tissue disorders: muscle weakness, rhabdomyolysis.

Renal and urinary disorders: symptoms of nephrogenic diabetes insipidus, impairment of renal function, permanent changes in the kidney, nephrotic syndrome, histological renal changes with interstitial fibrosis after long term treatment, polyuria, polydipsia.

Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy) (see Section 4.4).

Reproductive system and breast disorders: sexual dysfunction.

General disorders and administration site conditions: sudden unexplained death, oedema, asthenia, lethargy, thirst, fatigue, and malaise can occur due to lithium toxicity.

Other:
Some adverse events will be seen when Lithium levels are raised - for symptoms see section 4.9 Overdose.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Lithium carbonate has a narrow therapeutic window. Symptoms of lithium overdose (lithium intoxication) can occur due to intercurrent illness, iatrogenic causes, and self poisoning.

In patients with a raised lithium concentration, the risk of toxicity is greater in those with the following underlying medical conditions: hypertension; diabetes; congestive heart failure; chronic renal failure; schizophrenia; Addison's disease.

Any overdose in a patient who has been taking chronic lithium therapy should be regarded as potentially serious.

Acute overdosage

A single acute overdose usually carries low risk and patients tend to show mild symptoms only, irrespective of their serum lithium concentration. However more severe symptoms may occur after a delay if lithium elimination is reduced because of renal impairment, particularly if a slow-release preparation has been taken. The fatal dose, in a single overdose, is probably over 5g.

Acute overdosage in a patient on chronic lithium therapy

If an acute overdose has been taken by a patient on chronic lithium therapy, this can lead to serious toxicity occurring even after a modest overdose as the extravascular tissues are already saturated with lithium.

Symptoms
The onset of symptoms may be delayed, with peak effects not occurring for as long as 24 hours, especially in patients who are not receiving chronic lithium therapy or following the use of a sustained release preparation.

Mild: Nausea, diarrhoea, blurred vision, polyuria, light headedness, fine resting tremor, muscular weakness and drowsiness.

Moderate: Increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, choreoathetoid movements, urinary or faecal incontinence, increasing restlessness followed by stupor. Hypernatraemia.

Severe: Coma, convulsions, cerebellar signs, cardiac dysrhythmias including sinoatrial block, sinus and junctional bradycardia and first degree heart block. Hypotension or rarely hypertension, circulatory collapse and renal failure.

Management

There is no known antidote to lithium poisoning.

In the event of accumulation, lithium should be stopped and serum estimation should be carried out every 6 hours. Special attention must be given to the maintenance of fluid and electrolyte balance, and also adequate renal function. Forced diuresis or diuretics are contra-indicated. Appropriate supportive care may include measures to control hypotension and convulsions.

All patients should be monitored for a minimum of 24 hours. The ECG should be monitored in symptomatic patients. Steps should be taken to correct hypotension.

Consider gastric lavage for non-sustained-release preparations if more than 4g has been ingested by an adult within one hour or definite ingestion of a significant amount by a child. Slow-release tablets do not disintegrate in the stomach and most are too large to pass up a lavage tube. Gut decontamination is not useful for chronic accumulation. Whole bowel irrigation may be helpful in patients ingesting large quantities of a slow-release preparation.
Note: Activated charcoal does not adsorb lithium.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in all patients with marked neurological features.

It is the most efficient method of lowering lithium concentrations rapidly but substantial rebound increases can be expected when dialysis is stopped, and prolonged, or repeated treatments may be required.

It should be considered also in acute, acute on chronic or chronic overdose in patients with severe symptoms regardless of serum lithium concentration; discuss with your local poisons service.

Note: Clinical improvement generally takes longer than reduction of serum lithium concentrations regardless of the method used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The precise mechanism of action of lithium as a mood-stabilising agent remains unknown, although many cellular actions of lithium have been characterised.

5.2 Pharmacokinetic properties

Lithium is excreted almost exclusively in the urine by the kidneys.

It crosses the placenta, and is excreted in breast milk.

The pharmacokinetics of lithium are extremely well documented. A single oral dose of CAMCOLIT 400 gives a peak plasma level approximately 2-3 hours later, with the level at 24 hours being approximately 40% of peak levels. The half-life of lithium varies considerably between formulations, but generally is considered to be about 12 to 24 hours following a single dose.

Half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not, therefore, be attained until 4 to 7 days after starting treatment.

5.3 Preclinical safety data

In animal studies, lithium has been reported to interfere with fertility, gestation and foetal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Maize Starch
Acacia
Magnesium Stearate
Sodium Laurilsulfate

Film Coating
Hypromellose
Macrogol 400
Opaspray M-1-7111B (Hypromellose and Titanium Dioxide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.
Keep container tightly closed to protect from moisture.

6.5 Nature and contents of container

Polypropylene containers of 56, 100 or 500 tablets, and for hospital use only, screw-cap amber glass bottles of 50 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Essential Pharma (M) Limited
Vision Exchange Building
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Central Business District
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8 MARKETING AUTHORISATION NUMBER

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