1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S5

PROPRIETARY NAME AND DOSAGE FORM

CAMCOLIT 250 (film-coated tablets)

CAMCOLIT 400 (film-coated tablets)

COMPOSITION

Each CAMCOLIT 250 film-coated tablet contains lithium carbonate.

Excipients: Hydroxypropyl methyl cellulose (hypromellose), macrogol 400, magnesium stearate, maize starch, pregelatanised maize starch.

Sugar free

Each CAMCOLIT 400 film-coated tablet contains lithium carbonate.

Excipients: Acacia, hydroxypropyl methyl cellulose (hypromellose), macrogol 400, magnesium stearate, maize starch, Opaspray, sodium lauryl sulphate.

Sugar free

CATEGORY AND CLASS

A 1.2 Central Nervous System Stimulants - Psychoanaleptics or Antidepressants

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Investigations into the action of lithium are hampered by the lack of agreement of the aetiology of affective disorders. Three main mechanisms have been proposed:

1. Lithium interferes with the active transport of cations across nerve cell membranes.
2. It reduces the activity of non-adrenergic neurones in the brain.
3. It influences the balance and distribution of electrolytes and water in the various body compartments.

Pharmacokinetic properties

Distribution

The distribution space of lithium approximates that of total body water.

Elimination

Lithium is primarily excreted in urine, with insignificant excretion in faeces.

Renal clearance of lithium is proportional to its plasma concentration.

INDICATIONS

CAMCOLIT is indicated for the treatment and prevention of relapse of mania and manic-depressive illness.

CONTRAINDICATIONS

CAMCOLIT is contraindicated in:

- Patients with hypersensitivity to the active ingredient or to any of the excipients in CAMCOLIT (see COMPOSITION).
- Patients with renal disease, cardiac disease, Addison's disease.

- Patients with renal or cardiac failure, evidence of brain damage or a low sodium intake.
- Pregnancy and breastfeeding (see HUMAN REPRODUCTION).
- Patients with congenital long QT syndrome.
- Concomitant medicines known to prolong QT interval.

WARNINGS AND SPECIAL PRECAUTIONS

Lower doses of CAMCOLIT may be required with diuretic therapy as lithium clearance is reduced.

Serum lithium concentrations may increase during concomitant therapy with non-steroidal anti-inflammatory drugs possibly resulting in lithium toxicity. Serum lithium concentrations therefore should be monitored more frequently if a NSAID is initiated or discontinued.

Patients should be euthyroid before CAMCOLIT therapy is started.

Discontinue CAMCOLIT 24 hours before surgery.

CAMCOLIT toxicity is closely related to plasma lithium levels and can occur at doses close to therapeutic levels. Facilities for prompt and accurate plasma lithium determinations should be available before initiating therapy.

ACE-inhibitors and ARB's may raise serum lithium levels in some patients, especially the elderly or patients with renal impairment (see INTERACTIONS).

Raised plasma levels of ADH may occur during treatment.

Plasma lithium levels above 3,0 mmol/l may produce a complex clinical picture, involving multiple organs and organ systems. Plasma lithium levels should not be permitted to exceed 2,0 mmol/l during the acute treatment phase or 1,5 mmol/l during maintenance therapy.

Long term treatment with CAMCOLIT may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of CAMCOLIT, including episodes of acute CAMCOLIT toxicity may enhance these changes. The minimum clinically effective dose of CAMCOLIT should always be used. Patients should only be maintained on CAMCOLIT after 3 to 5 years if, on assessment, benefit persists.

Since CAMCOLIT can impair thyroid function, it is desirable in patients being treated prophylactically that some screening test of thyroid function, such as the protein-bound iodine test, be carried out at about three-monthly intervals. Many of the initial symptoms of hypothyroidism are similar to symptoms seen in depression, and hence it is difficult to differentiate except by some such screening of thyroid function. Thyrotoxicosis has also been reported.

In all cases plasma lithium levels should be determined frequently and even when consistent levels have been achieved in prophylaxis, should be monitored at least every 10 weeks.

The ability to tolerate CAMCOLIT is considerably increased during the acute manic phase and decreases markedly when manic symptoms subside.

CAMCOLIT decreases sodium re-absorption by the renal tubules, which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2 500 to 3 000 ml) at least during the initial stabilisation period.

When sodium intake is lowered, CAMCOLIT excretion is slower and severe intoxication may ensue. Thus, CAMCOLIT should not be given to patients on a salt-free diet. In pregnancy, concomitant use of natriuretics (diuretics) and low-sodium diets is the most common cause of maternal and neonatal CAMCOLIT intoxication.

Decreased tolerance to CAMCOLIT has been reported to ensue from protracted sweating or diarrhoea, and if such occur, supplemental fluid and salt should be administered.

The physician should be alert for possible thyroid involvement. Diffuse non-toxic goitre has been reported in a small number of patients on maintenance therapy with CAMCOLIT and in one baby born to a lithium treated mother.

Symptoms of nephrogenic diabetes insipidus are particularly prevalent in patients receiving concurrent treatment with tricyclic anti-depressants (see INTERACTIONS).

Effects on ability to drive and use machines

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

INTERACTIONS

Lower doses of CAMCOLIT may be required with diuretic therapy as lithium clearance is reduced.

Acetazolamide increases renal elimination of CAMCOLIT and lowers serum levels.

Serum lithium concentrations may increase during concomitant therapy with non-steroidal anti-inflammatory drugs possibly resulting in lithium toxicity. Serum lithium concentrations therefore should be monitored more frequently if a NSAID is initiated or discontinued.

Metronidazole impairs renal elimination of CAMCOLIT and increases serum lithium concentrations, causing toxicity.

Combination of CAMCOLIT with antidepressants such as SSRI's (Selective Serotonin Reuptake Inhibitors) and tricyclic antidepressant agents may increase the risk of side effects.

Carbamazepine, clonazepam and possibly phenytoin may cause neurotoxicity without a change in serum lithium levels.

Methyldopa can increase CAMCOLIT toxicity without any change in serum lithium levels.

Combination of CAMCOLIT with other anti-psychotics may increase the risk of side effects, particularly extra-pyramidal symptoms.

Diltiazem or verapamil may cause unpredictable neurotoxic side effects and potential for bradycardia without change in serum lithium concentration.

Caffeine and other xanthine derivatives can increase the renal excretion of CAMCOLIT and potentially reduce serum lithium levels.

Sodium salts, particularly bicarbonate and chloride, may also reduce stable serum lithium concentrations by increasing renal excretion. Dietary changes that markedly change salt intake should be avoided.

ACE-inhibitors and ARB's (Angiotensin Receptor Blockers) may raise serum lithium levels of CAMCOLIT, especially in the elderly or patients with renal impairment.

Symptoms of nephrogenic diabetes insipidus are particularly prevalent in patients receiving concurrent treatment with tricyclic antidepressants.

HUMAN REPRODUCTION

Pregnancy

There is epidemiological evidence to suggest that CAMCOLIT is harmful during pregnancy. Lithium crosses the placental barrier, and can be harmful to the foetus.

Lactation

Infants of mothers on CAMCOLIT should be bottle fed, as lithium is present in the breast milk (see CONTRAINDICATIONS). CAMCOLIT should not be used in pregnancy and lactation (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

Treatment of acute mania

The required daily dosage may be administered at the discretion of the clinician, either in divided doses or as a single daily dose. Treatment of mania 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 and 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 CAMCOLIT.

Details of Initial Dosing

1 000 mg to 1 500 mg of CAMCOLIT is administered daily for the first five or seven days. A blood sample for plasma lithium estimation is taken 12 hours after the last dose on the fifth or seventh 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 CAMCOLIT should be decided in the light of age and mass of the patient; young patients often require a dose higher than average and older patients a lower dose.

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 of CAMCOLIT made as a result of the levels actually obtained.

Most of the above applies to the treatment of hypomania as well as mania, but the patient (if not too ill) can be started on treatment as an out-patient provided that facilities for periodic plasma lithium monitoring are available and assays are initiated within 1 week.

Use in elderly: *As* for prophylaxis above, but 12-hour lithium levels should be kept in the range of 0,4 to 0,7 mmol/l, as toxic symptoms are likely with plasma concentrations above 1,0 mmol/l.

Use in children: Not recommended.

SIDE EFFECTS

Side effects are listed in terms of their frequency as follows:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000 < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Adverse reactions are seldom encountered at plasma lithium levels below 1,0 mmol/l except in the occasional patient unusually sensitive to CAMCOLIT. Mild to moderate toxic reactions may occur at levels from 1,5 to 2,5 mmol/l, and moderate to severe reactions may occur at levels from 2,0 to 2,5 mmol/l depending upon the individual response to CAMCOLIT.

Patients on therapeutic doses of CAMCOLIT may complain of fatigue and muscular weakness. Fine hand tremor, slurred speech, polyuria, and polydipsia may occur during initial therapy for the acute manic phase, and may persist throughout treatment.

Transient and mild nausea and general discomfort may also appear during the first few days of CAMCOLIT administration. Toxic signs are rarely seen in patients stabilised on maintenance doses.

Diarrhoea, vomiting, drowsiness, muscular weakness and lack of co-ordination may be early signs of CAMCOLIT intoxication, and can occur at lithium levels below 2,0 mmol/l. At higher levels, ataxia, giddiness, tinnitus, blurred vision and a large output of dilute urine may be seen.

While most side effects are more common during the first week or two of treatment and usually disappear when the dose is reduced, thirst, excessive urination and tremor may persist.

The following adverse reactions have been reported and appear to be related to the plasma lithium levels:

System organ Class	Frequency	Side Effect
Cardiac disorders	Less frequent	Cardiac dysrhythmia ECG changes: Reversible flattening; iso-electricity or inversion of T waves, sinus node dysfunction
	Frequency unknown	Oedema, hypertension, peripheral circulatory collapse
Immune system	Less frequent	Leukocytosis
	Frequency unknown	Increase in antinuclear antibodies
Vascular disorders	Frequency unknown	Allergic vasculitis, hypotension
Nervous system disorders	Frequent	Fine hand tremor
	Less frequent	Syncope (blackout spells), stupor, confusion, slurred speech, dizziness
	Less frequent	Nystagmus

	Frequency unknown	EEG Changes: Diffuse slowing, widening of the frequency spectrum, potentiation and disorganisation of background rhythm. A dazed feeling may occur but disappears after stabilisation, epileptiform seizures, vertigo, muscular rigidity, incontinence of urine and faeces, somnolence, psychomotor retardation, restlessness, myasthenia gravis
Eye disorders	Less frequent	Blurred vision Exophthalmos Transient scotoma (blind spot)
Gastrointestinal disorders	Frequent	Diarrhoea, nausea
	Frequency unknown	Vomiting, dry mouth, excessive salivation, gastritis
Renal and urinary disorders	Frequent	Polydipsia
	Less frequent	Acquired nephrogenic diabetes insipidus accompanied by excessive thirst Albuminuria
	Frequency unknown	Polyuria, glycosuria
Skin and subcutaneous tissue disorders	Less frequent	Occurrence or exacerbation of acne
	Frequency unknown	Thinning of hair, alopecia, occurrence or exacerbation of psoriasis, pruritus, rash

Musculoskeletal and connective tissue disorders	Less frequent	Muscle hyperirritability, twitching, muscle weakness, choreoathetotic movements, muscular rigidity
Endocrine disorders	Less frequent	Hypothyroidism, hyperthyroidism
	Frequency unknown	Goitre formation Thyrotoxicosis, hyperparathyroidism, parathyroid adenoma Lowering of the PBI (plasma protein-bound iodine), increased I^{131} intake
Metabolism and nutrition disorders	Frequent	Weight gain
	Frequency unknown	Transient hyperglycaemia, hypercalcaemia, hypermagnesaemia, anorexia
General disorders	Less frequent	Thirst
	Less frequent	Headache
	Frequency unknown	Fatigue, lethargy, asthenia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Symptoms of early toxicity include vomiting, diarrhoea, nausea, abdominal pain, coarse tremor of the hands, loss of co-ordination, muscle weakness, muscle hyperirritability, choreoathetoid movements, confusion, drowsiness, dysarthria, loss of appetite, anorexia, ataxia, giddiness, tinnitus, blurred vision, urinary or faecal incontinence.

Symptoms of severe CAMCOLIT toxicity include hyperreflexia, attacks of hyperextension of the limbs, myoclonus, severe trembling**,** epileptic seizures, speech disturbances, metallic taste, toxic

psychosis, syncope, polyuria, electrolyte imbalance, dehydration, renal and/or circulatory failure, hypotension or rarely hypertension, coma. Deaths have been reported.

Treatment

In these cases, withdrawal of the drug and conservative treatment is indicated. Lithium levels should be estimated every 6 hours. Gastric lavage can be carried out if recently ingested.

Special attention must be given to the maintenance of fluid and electrolyte balance, and also adequate renal function. Sodium-depleting diuretics should not be used in any circumstances. If the serum lithium level is above 4,0 mmol/l, or if there is deterioration in the patient's condition, or if the serum lithium concentration is not falling at a rate equivalent to a half-life of less than 30 hours, peritoneal dialysis or haemodialysis should be instituted promptly. This should be continued until the serum and dialysis fluid are free of lithium. Serum lithium levels should be monitored for at least another 7 days thereafter, as a rebound rise is possible due to delayed diffusion from the tissues. If haemodialysis facilities are not available, peritoneal dialysis is secondary in choice, but may be used.

IDENTIFICATION

CAMCOLIT 250:	White, film-coated convex tablets, engraved “CAMCOLIT” around one face of tablet and breakline on the reverse.
CAMCOLIT 400:	White, film-coated convex tablets, with a breakline on one side and “CAMCOLIT S” engraved on the other side.

PRESENTATION

CAMCOLIT 250: 100 and 1 000 tablets are packed in a snap secure white polypropylene container, with a snap secure white polyethylene cap and a white polyethylene Jayfilla wad.

CAMCOLIT 400: 100 and 500 tablets are packed in a snap secure white polypropylene container, with a snap secure white polyethylene cap and a white polyethylene Jayfilla wad.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store in a cool, dry place at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION/REFERENCE NUMBER

CAMCOLIT 250: B1260 (Act 101/1965)

CAMCOLIT 400: L/1.2/0161

NAME AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration:

CAMCOLIT 250: Old Medicine

CAMCOLIT 400: 09 August 1982

Date of the most recent amendment to the professional information as approved by the authority:

20 April 2012

Botswana:	S2
Camcolit 250:	BOT1001689
Camcolit 400:	BOT1001690

Namibia:	NS3
Camcolit 250:	05/1.2/0440
Camcolit 400:	90/1.2/00671

ZA_CAMCTAB_1204_02