

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Priadel 400mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 400 mg lithium carbonate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, circular, biconvex tablets engraved "PRIADEL" on one side and a score line on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- In the management of acute manic or hypomanic episodes.
- In the management of episodes of recurrent depressive disorders where treatment with other antidepressants has been unsuccessful.
- In the prophylaxis against bipolar affective disorders.
- Control of aggressive behaviour or intentional self harm.

4.2 Posology and method of administration

Dosage must be individualised depending on serum lithium levels and clinical response. The dosage necessary to maintain serum lithium levels within the therapeutic range varies from patient to patient. The minimum effective dose should be sought and maintained.

A simple treatment schedule has been evolved which except for some minor variations should be followed whether using Priadel therapeutically or prophylactically. The minor variations to this schedule depend on the elements of the illness being treated and these are described later.

1. In patients of average weight (70 kg) an initial dose of 400 - 1,200 mg of Priadel may be given as a single daily dose in the morning or on retiring. Alternatively, the dose may be divided and given morning and evening. The tablets should not be crushed or chewed. When changing for other lithium preparations serum lithium levels should first be checked, then Priadel therapy started at a daily dose as close as possible to the dose of the other form of lithium. As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) a change of product should be regarded as initiation of new treatment.
2. Four to a maximum of seven days after starting treatment serum lithium levels should be measured.
3. The objective is to adjust the Priadel dose so as to maintain the serum lithium level permanently within the diurnal range of 0.5 - 1.5 mmol/l. Blood samples should be taken 12 or 24 hours after the previous dose of Priadel, just before the next dose is due, to measure the serum lithium level at its trough. "Target" serum lithium concentrations at 12 and 24 hours are shown in the table below. "Target" serum lithium concentration (mmol/l) At 12 hours At 24 hours
Once daily dosage 0.7 – 1.0 0.5 – 0.8
Twice daily dosage 0.5 – 0.8

The tablets have score lines, therefore they can be divided accurately to provide smaller dosage requirements. Serum lithium levels should be monitored weekly until stabilisation is achieved.

4. Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. Following stabilisation of serum lithium levels, the period between subsequent estimations can be increased gradually but should not normally exceed two to three months. Additional measurements should be made following alteration of dosage, on development of intercurrent disease, signs of manic or depressive relapse, following significant change in sodium or fluid intake, or if signs of lithium toxicity occur (see section 4.9).

5. Whilst a high proportion of acutely ill patients may respond within three to seven days of the commencement of Priadel therapy, Priadel should be continued through any recurrence of the affective disturbance. This is important as the full prophylactic effect may not occur for 6 to 12 months after the initiation of therapy.

6. In patients who show a positive response to Priadel therapy, treatment is likely to be long term. Careful clinical appraisal of the patient should be exercised throughout medication (see section 4.4).

Prophylactic treatment of bipolar affective disorders and control of aggressive behaviour or intentional self-harm

It is recommended that the described treatment schedule is followed.

Treatment of acute manic or hypomanic episodes and recurrent depressive disorders

It is likely that a higher than normal Priadel intake may be necessary during an acute phase and divided doses would be required here. Therefore, as soon as control of mania or depression is achieved, the serum lithium level should be determined and it may be necessary, dependent on the results, to lower the dose of Priadel and re-stabilise serum lithium levels. In all other details the described treatment schedule is recommended.

Elderly

Elderly patients, or those below 50 kg in weight, often require lower lithium dosage to achieve therapeutic serum levels (see section 4.4). Starting doses of 200 mg to 400 mg are recommended. Dosage increments of 200 to 400 mg every 3 to 5 days are usual. Total daily doses of 800 to 1800 mg may be necessary to achieve effective blood lithium levels of 0.8 to 1.0 mmol/l. For prophylaxis, the dosage necessary to reach a blood lithium level of 0.4 to 0.8 mmol/l is generally in the range of 600 to 1200 mg/day.

Paediatric population

The use in children is not recommended.

Renal impairment

In patients with mild and moderate renal insufficiency treated with lithium, serum lithium levels must be closely monitored and the dose should be adjusted accordingly to maintain serum lithium levels within the recommended range (see section 4.4). Lithium is contraindicated in patients with severe renal insufficiency (see section 4.3).

Method of administration

For oral use. The prolonged-release tablets should not be crushed or chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Cardiac insufficiency;
- Severe renal insufficiency;
- Addison's disease;
- Untreated hypothyroidism;
- Breast-feeding;
- Brugada syndrome or family history of Brugada syndrome (see section 4.4).

4.4 Special warnings and precautions for use

General

When considering Priadel therapy, it is necessary to ascertain whether patients are receiving lithium in any other form. If so, check serum levels before proceeding.

The minimum clinically effective dose of lithium should always be used (see section 4.2).

Clear instructions regarding the symptoms of impending toxicity should be given by the physician to patients receiving long term lithium therapy (see section 4.9). At the first sign of toxicity, the patient should consult a physician and lithium levels should be checked.

Monitoring recommendations

Before starting treatment with lithium renal function, cardiac function and thyroid function should be evaluated. Patients should be euthyroid before initiation of lithium therapy. Lithium therapy is contraindicated in patients with severe renal insufficiency or cardiac insufficiency (see section 4.3).

Renal, cardiac and thyroid functions should be re-assessed regularly during treatment with lithium.

For monitoring recommendations of lithium serum levels, see section 4.2.

Renal impairment and renal tumours

Since lithium is primarily excreted via the renal route, significant accumulation of lithium may occur in patients with renal insufficiency. Therefore, if patients with mild or moderate renal impairment are being treated with lithium, serum lithium levels should be closely monitored (see section 4.2) and the dose should be adjusted accordingly. If very regular and close monitoring of serum lithium levels and plasma creatinine levels is not possible, lithium should not be prescribed in this population. Lithium is contraindicated in patients with severe renal insufficiency (see section 4.3).

Patients should also be warned to report if polyuria or polydipsia develop.

In patients who develop polyuria and/or polydipsia (see section 4.8), renal function should be monitored in addition to the routine serum lithium assessment.

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).

Fluid/electrolyte balance

If episodes of nausea, vomiting, diarrhoea, excessive sweating and/or other conditions leading to salt/water depletion (including severe dieting) occur, lithium dosage should be closely monitored and dosage adjustments made as necessary. Caution should be exercised to ensure that diet and fluid intake are normal in order to maintain a stable electrolyte balance. This may be of special importance in very hot weather or work environment. Infectious diseases including colds, influenza, gastro-enteritis and urinary infection may alter fluid balance and thus affect serum lithium levels. Treatment discontinuation should be considered during any intercurrent infection.

Risk of convulsions

The risk of convulsions may be increased in case of co-administration of lithium with drugs 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 caution should be exercised in patients with risk factors for QT interval prolongation (e.g. uncorrected hypokalemia, bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QT interval (see sections 4.5 and 4.8).

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 is not recommended in patients with known Brugada 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

In patients who have undergone bariatric surgery, a lower maintenance dose of lithium may be required. Lithium levels should be closely monitored due to the risk of lithium toxicity until weight has stabilized.

Elderly

Elderly patients are particularly liable to lithium toxicity and may exhibit adverse reactions at serum levels ordinarily tolerated by younger patients. Caution is also advised since lithium excretion may be reduced in the elderly due to age related decrease in renal function (see sections 4.2 and 5.2).

Excipients

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Serum lithium levels may be increased if one of the following drugs is co-administered. When appropriate, either lithium dosage should be adjusted or concomitant treatment stopped.

- Thiazide diuretics may reduce lithium renal clearance, potentially leading to lithium intoxication. If a thiazide diuretic has to be used, lithium dosage should first be reduced. Loop diuretics seem less likely to increase lithium levels;
- Other drugs affecting electrolyte balance, e.g. steroids, may alter lithium excretion and should therefore be avoided;
- Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase (COX) 2 inhibitors;
- Angiotensin-converting enzyme (ACE) inhibitors;
- Angiotensin II receptor antagonists;
- Metronidazole may reduce lithium renal clearance;
- Tetracyclines. Serum lithium levels may be decreased due to an increase in lithium renal clearance in case of concomitant administration of one of the following drugs:
 - Osmotic diuretics and carbonic anhydrase inhibitors;
 - Xanthine (theophylline, caffeine);
 - Sodium bicarbonate;
 - Calcitonin;
 - Empagliflozin;
 - Dapagliflozin. Co-administration of the following drugs may increase the risk of neurotoxicity:
 - Calcium channel blockers may lead to a risk of neurotoxicity with symptoms such as ataxia, confusion and somnolence. Lithium concentrations may be increased;
 - 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 may lead to dizziness, somnolence, confusion and cerebellar symptoms such as ataxia;
 - Methyldopa;
 - Triptan derivatives and/or serotonergic antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs) (such as fluoxetine and fluvoxamine) may result in occurrence of serotonin syndrome, which requires immediate treatment discontinuation. The serotonin syndrome is a potentially life-threatening adverse drug reaction, which is caused by an excess in serotonin (e.g. from overdose or concomitant use of serotonergic drugs), necessitating hospitalisation or even causing death. Symptoms may include:
 - Mental status change (agitation, confusion, hypomania, eventually coma);
 - Neuromuscular abnormalities (myoclonus, tremor, hyperreflexia, rigidity, akathisia);
 - Autonomic hyperactivity (hypo or hypertension, tachycardia, shivering, hyperthermia, diaphoresis);
 - Gastrointestinal symptoms (diarrhoea). Strict adherence to the recommended doses is an essential factor for the prevention of the occurrence of this syndrome. Other:
- Caution is advised if lithium is co-administered with other drugs that prolong the QT interval (see sections 4.8 and 4.9) e.g. Class IA (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone) antiarrhythmic agents, cisapride, antibiotics such as erythromycin, antipsychotics such as thioridazine or amisulpride;
- Caution is advised if lithium is co-administered with drugs that lower the epileptic threshold (see section 4.4), e.g. antidepressants such as SSRIs, tricyclic antidepressants, antipsychotics, anaesthetics, theophylline.
- Topiramate: In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the

pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. There have been reports on lithium toxicity when concurrently administered with topiramate. Lithium levels should be closely monitored when co-administered with topiramate.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. It may be harmful to the fetus in human pregnancy. Cardiac, especially Ebstein anomaly, and other malformations have been reported. Therefore, a pre-natal diagnosis such as ultrasound examination is strongly recommended.

If it is considered essential to maintain lithium treatment during pregnancy, serum lithium levels should be closely monitored 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, including symptoms such as lethargy, flaccid muscle tone, or hypotonia. Careful clinical observation of the neonate exposed to lithium during pregnancy is recommended and lithium levels may need to be monitored as necessary.

Women of child-bearing potential

Women of child-bearing potential should use effective contraceptive methods during treatment with lithium.

Breast-feeding

Lithium is secreted in breast milk, and there have been case reports of neonates showing signs of lithium toxicity (see Pregnancy). Therefore lithium should not be used during breast-feeding (see section 4.3). A decision should be made whether to discontinue lithium therapy or to discontinue breast-feeding, taking into account the importance of the drug to the mother and the importance of breast-feeding to the infant.

Fertility

Published studies in rats exposed to lithium have reported spermatogenesis abnormalities that may lead to impairment of fertility. This risk may also potentially apply to humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Since lithium may slow reaction time, and considering the adverse reactions profile of lithium (see section 4.8), patients should be warned of the possible hazards when driving or using machines.

4.8 Undesirable effects

Side effects are usually related to serum lithium concentration and are infrequent at levels below 1.0 mmol/l. The adverse reactions usually subside with a temporary reduction or discontinuation of lithium treatment. Mild gastrointestinal effects such as nausea, a general discomfort and vertigo, may occur initially, but frequently disappear after the first few days of lithium administration. Fine hand tremors, polyuria and mild thirst may persist.

Blood and lymphatic system disorders

Leucocytosis.

Endocrine disorders

Long-term adverse effects may include thyroid function disturbances such as euthyroid goitre and/or hypothyroidism. Rarely hyperthyroidism may also occur. Hypermagnesaemia has been reported.

Very frequent: Hypercalcaemia

Frequency not known: Hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia

Metabolism and nutrition disorders

Weight increase.

Psychiatric disorders

Confusion, delirium.

Nervous system disorders

Tremor especially fine hand tremors, dysarthria, myoclonus, benign intracranial hypertension (see section 4.4).
Vertigo, impaired consciousness, abnormal reflexes, convulsions (see section 4.4 and 4.5), extrapyramidal disorders, encephalopathy, cerebellar syndrome (usually reversible), nystagmus.
The above symptoms may result in fall.
Peripheral neuropathy may occur on long-term treatment and is usually reversible at cessation of lithium.
Memory impairment may occur during long term use.
Serotonin syndrome.
Neuroleptic malignant syndrome.

Eye disorders

Eye irritation (reversible in most cases); optic disc swelling, in some cases without increased intracranial pressure; papilloedema leading to possible visual impairment (generally reversible); exophthalmos (not always associated with thyroid disorders)

Cardiac disorders

QT prolongation, sometimes associated with ventricular tachycardia or torsades de points, which may result in ventricular fibrillation or cardiac arrest and sudden death. Cardiac arrhythmia mainly bradycardia, sinus node dysfunction, ECG changes such as reversible flattening or inversion of T-waves, AV block, cardiomyopathy.
Frequency not known: Brugada syndrome (Unmasking/aggravation)

Gastrointestinal disorders

Abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, salivary hypersecretion, dry mouth.

Skin and subcutaneous tissue disorders

Acne or acneiform eruptions, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers.
Frequency not known: Lichenoid drug reaction.
Frequency not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders

Muscle weakness, rhabdomyolysis.

Renal and urinary disorders

Polydipsia and/or polyuria and nephrogenic diabetes insipidus have been reported (see section 4.4). This is usually reversible on lithium withdrawal.
Long term treatment with lithium may result in permanent changes in kidney histology, formation of renal microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy) (see section 4.4) and impairment of renal function. High serum concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes. Cases of nephrotic syndrome have been reported.

General disorders and administration site conditions

Peripheral oedema. Urticaria and angioedema, attributed to some excipients such as acacia (or acacia gum).

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

Symptoms

Symptoms of lithium intoxication include:

- Gastrointestinal disorders: increasing anorexia, diarrhoea and vomiting;
- Nervous system disorders: Encephalopathy, cerebellar syndrome with symptoms such as muscle weakness, lack of coordination, drowsiness or lethargy, giddiness, ataxia, nystagmus, coarse tremor. Tinnitus, blurred vision, dysarthria, twitching, myoclonus, extrapyramidal disorders;
- Other: ECG changes (flat or inverted T waves, QT prolongation), AV block, dehydration and electrolyte disturbances. At blood levels above 2 - 3 mmol/l, there may be a large output of dilute urine and renal insufficiency, with increasing confusion, convulsions, coma and death. Management There is no specific antidote to

lithium. In the event of lithium overdose, lithium should be discontinued and lithium serum levels monitored closely. Supportive treatment should be initiated, which includes correction of fluid and electrolyte balance, if necessary. Diuretics should not be used (see section 4.5). Haemodialysis is the treatment of choice for severe lithium intoxication (especially in patients manifesting with severe nervous system disorders), or in cases of overdose accompanied by renal impairment.

Haemodialysis should be continued until there is no lithium in the serum or dialysis fluid. Serum lithium levels should be monitored for at least another week to take account of any possible rebound in serum lithium levels as a result of delayed diffusion from the body tissues.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Lithium, Antipsychotics, ATC code: N05AN01

Mood-stabilizing agent

Lithium is an alkali metal available for medical use as lithium carbonate or lithium citrate. The exact mechanism of action of lithium in the treatment of bipolar disorders is not known. However, lithium modifies the production and turnover of certain neurotransmitters, particularly serotonin, and it may also block dopamine receptors.

It modifies concentrations of some electrolytes, particularly calcium and magnesium, and it may reduce thyroid activity.

5.2 Pharmacokinetic properties

Absorption

Lithium is rapidly absorbed from the gastrointestinal tract.

Steady-state lithium levels may not be obtained until 4 - 6 days.

Time to peak serum level for controlled prolonged-release Priadel tablets is about 2 hours and approximately 90% bioavailability would be expected.

Distribution

Lithium has a low volume of distribution (0.7 to 0.9 l/kg).

It is not bound to plasma proteins.

Lithium crosses the placenta and is excreted in breast milk.

Biotransformation

Lithium is not metabolized in the liver.

Elimination

Lithium is excreted primarily by the kidneys (>95% of the dose).

Elimination half-life ranges from 18 to 36 hours.

Lithium can be eliminated by haemodialysis.

Special populations

Elimination half-life may be increased in elderly patients due to age related decrease in renal function and also in patients with renal impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Teratogenicity

Cardiac, especially Ebstein anomaly, and other malformations have been reported with lithium in human pregnancies (see section 4.6).

Impairment of fertility

Published studies in rats exposed to lithium have reported spermatogenesis abnormalities that may lead to impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol distearate
Mannitol (E 421)
Acacia spray-dried
Sodium laurilsulfate
Magnesium stearate
Maize starch
Sodium starch glycolate (type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVdC/aluminium blister strips, each strip containing 10 tablets. Ten strips are packed in a cardboard outer.

Hospital packs of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA22587/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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