NEW ZEALAND DATA SHEET

1. PRIADEL PROLONGED RELEASE TABLETS 400 MG

Priadel prolonged release tablets 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg lithium carbonate.

For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Prolonged release tablets.

White circular, bi-convex tablets engraved PRIADEL on one side, scored on the other side. Each tablet contains 400 mg Lithium Carbonate Ph Eur in a controlled release dosage form.

PRIADEL tablets are scored; therefore they can be divided accurately to provide dosage adjustments of 200 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Treatment of mania and hypomania.
2. Treatment of patients with recurrent bipolar depression, for which treatment with other antidepressants has been unsuccessful.
3. Prophylactic treatment of recurrent affective disorders.

4.2 Dosage and method of administration

Dose

The following dosing and monitoring schedule should be followed whether using PRIADEL therapeutically or prophylactically.

Initial dose

In patients of average weight (70 kg) an initial dose of 1-3 tablets (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 patients age and weight should be reviewed as part of initial dose selection. Older patients often require lower doses.

Ongoing dose

Four to five days after starting treatment (and never longer than one week) a blood sample should be taken for the estimation of serum lithium level.

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. The serum level should not exceed 1.5 mmol/L.

In practice, the blood sample should be taken 12 or 24 hours after the previous dose of PRIADEL. “Target” serum lithium concentrations at 12 and 24 hours are shown in the table.

“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	

Lithium carbonate has narrow therapeutic window. The dose required for treatment must be titrated and adjusted on the basis of regular monitoring of the serum concentration. Dosage must be individualised depending on serum lithium levels and clinical response.

Optimal maintenance serum lithium levels and dosage necessary to maintain serum lithium levels varies from patient to patient. The minimum effective dose should be used.

Serum lithium levels should be monitored weekly until stabilisation is achieved.

Monitoring

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 three months. Serum lithium levels should be measured at regular intervals for the duration of treatment.

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. More frequent monitoring is also required if patients are receiving any interacting drug for example drug treatment that affects renal clearance of lithium or drugs that affect electrolyte balance (e.g NSAIDS, diuretics, see section 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interaction).

Toxic symptoms of lithium are usually associated with serum lithium levels exceeding 1.5 mmol/L. Toxic effects can occur at lower concentrations. In the event of toxicity, lithium should be withdrawn immediately (see section 4.4 Special warnings and precautions).

Duration of treatment

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.

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 treatment (see section 4.4 Special warnings and precautions for use.)

Switching between lithium preparations

When changing from other lithium preparations, serum lithium levels should first be checked, then PRIADEL therapy commenced 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.

Treatment of acute mania, hypomania and recurrent bipolar depression

It is likely that a higher than normal dose of PRIADEL may be necessary during an acute phase and divided doses would be required here. As a general rule the monitoring should maintain serum levels at 0.8-1.2 mmol/l until acute symptoms have been controlled. In all other details the described treatment schedule is recommended. The dosage needed may vary from patient to patient. Serum lithium levels should be monitored (see above) and should not exceed 1.5 mmol/L. Once clinical control is achieved, dosage should be reduced to the prophylactic dose to achieve maintenance lithium levels.

Prophylactic treatment of recurrent affective disorders

It is recommended that the described treatment schedule is followed.

Withdrawal

In the event of toxicity, lithium should be withdrawn immediately. 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 at least 2 weeks) to prevent the risk of relapse.

Special populations

Use in renal impairment

Since lithium is primarily excreted via the renal route, significant accumulation of lithium may occur in patients with renal insufficiency. This increases the risk of toxicity.

Lithium is contraindicated in patients with significant renal disease (see Section 4.3 Contraindications).

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.

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.

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

Use in the elderly

In elderly patients or those below 50 kg in weight, it is recommended that the starting dose be one tablet (400 mg). Elderly patients may be more sensitive to undesirable effects of lithium and may also require lower doses in order to maintain normal serum lithium levels. Lower target lithium levels may be suitable. It follows therefore that long term patients often require a reduction in dosage over a period of years.

Paediatric population

Use in children and adolescents is not recommended.

Method of Administration

PRIADEL tablets should be taken with food, as this causes less nausea than on an empty stomach. The tablets should not be crushed, chewed or swallowed with hot liquids.

The prolonged release tablets should be taken at the same time every day. A double dose to make up for a dose that has been missed should not be taken. The tablets have break lines and therefore they can be divided accurately to provide dosage requirements as small as 200 mg.

4.3 Contraindications

- Patients with significant cardiovascular or renal disease
- Conditions associated with hyponatraemia, such as Addison's disease, dehydrated or severely debilitated patients, and patients on low sodium diets
- Known hypersensitivity to lithium or any of the excipients in PRIADEL tablets
- Breastfeeding
- Untreated hypothyroidism
- Patients with Brugada Syndrome or family history of Brugada Syndrome

4.4 Special warnings and precautions for use

Hypercalcaemia and Hyperparathyroidism

Systematic review indicates that about 10% of patients taking lithium long-term develop hypercalcaemia with or without hyperparathyroidism. Patients should be checked for parathyroid function prior to commencing treatment.

Serum calcium levels should be monitored at least yearly in all patients taking lithium. Monitoring should be more frequent if an abnormal result is found or the patient has a family history of endocrine disease.

If serum calcium levels are raised, the serum parathyroid level should be measured. If both parathyroid hormone levels and calcium levels are elevated, the patient should be referred for specialist treatment.

In cases of mild hypercalcaemia with normal parathyroid hormone levels, treatment may be continued if the benefits are considered to outweigh the risks, but calcium levels should be monitored more frequently.

If serum calcium levels rise above 11 mg/dL, lithium treatment should be stopped and calcium levels measured weekly for the next 4 weeks to ensure that levels drop back to normal.

Patients who have undergone parathyroidectomy in the past may experience recurrent hyperparathyroidism on lithium treatment; serum calcium and parathyroid hormone levels should be carefully monitored.

Lithium toxicity

Patients and family members should be warned of the signs and symptoms of lithium toxicity and taught to recognise the symptoms of early toxicity and, should these occur, to discontinue therapy and request medical aid at once (see section 4.9 Overdose).

Symptoms of lithium toxicity may include the following:

1. Gastro-intestinal: increasing anorexia, dehydration, diarrhoea and vomiting.
2. Central nervous system: muscle weakness, lack of co-ordination, drowsiness or lethargy progressing to giddiness and ataxia, tinnitus, blurred vision, dysarthria, confusion, nystagmus, coarse tremor and muscle twitching
3. Cardiovascular events such as QT/QTc prolongation

Elderly patients are particularly susceptible to lithium toxicity.

At blood levels above 2-3 mmol/L there may be a large output of dilute urine, with increasing disorientation, seizures, coma and death.

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. For monitoring recommendations of lithium serum levels (see section 4.2 Dosage and method of administration).

If toxic symptoms appear, patients should be instructed to immediately stop taking PRIADEL and to report for a serum lithium estimation.

Monitoring requirements

Pre-treatment

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.

Physical examination and laboratory testing are required prior to commencement of therapy and should be repeated at frequent intervals.

Since lithium is excreted primarily by the kidney, adequate renal function is essential in order to avoid lithium accumulation and intoxication. A creatinine clearance test or other renal function test should be performed before starting treatment and renal function monitored throughout treatment, especially where acute changes in renal function may occur. Lithium is contraindicated in patients with significant renal disease (see section 4.3 Contraindications).

Cardiac, thyroid and parathyroid (parathyroid hormone and serum calcium level) function should be assessed before commencing lithium treatment. Patients should be euthyroid before the initiation of lithium therapy (see section 4.3 Contraindications).

Reversible ECG changes e.g. T wave flattening, or inversion, cardiac arrhythmias and EEG changes have been reported with lithium treatment (see section 4.8 Undesirable effects). Use in patients with significant cardiovascular disease is contraindicated due to risk of precipitation of cardiac arrhythmia (section 4.3 Contraindications).

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.

On treatment

Renal function, cardiac function, thyroid and parathyroid function should be reassessed periodically and as clinically indicated throughout treatment.

Serum calcium levels should be monitored (see hypercalcaemia and hyperparathyroidism). Lithium may also cause hypermagnesemia.

Lithium levels

Continue to monitor serum lithium levels periodically (at least every three months following stabilisation). Increased monitoring frequency is required in circumstances where lithium levels may be increased.

For example:

- Dosage alteration or change of lithium 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.

Vomiting, diarrhoea, excessive sweating, conditions leading to salt/water depletion, intercurrent infection, fluid deprivation and drugs likely to upset electrolyte balance, such as diuretics, may all reduce lithium excretion thereby precipitating intoxication.

Caution should be exercised to ensure that diet and fluid intake are normal, maintaining a stable electrolyte balance. Infectious diseases including colds, influenza, gastro-enteritis and urinary infections may alter fluid balance and thus affect serum lithium levels. Serum lithium levels can also be impacted by very hot weather or working environments.

Patients should avoid low-salt dietary regimens or other dietary changes which may reduce sodium intake, or circumstances which may cause excessive sodium loss such as heavy exercise leading to excessive sweating as these may lead to increased lithium concentrations. The patient, therefore, should maintain a normal diet with adequate salt and fluid intake during therapy.

Lithium levels should be closely monitored during circumstances where levels may be increased, and the dose adjusted accordingly, or treatment discontinued.

Other

Lithium requirements may change during fever, infection, and when mood swings occur. Patients in a manic state seem to have increased tolerance to lithium which decreases when manic symptoms subside.

Renal impairment/nephrotoxicity

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. The minimum clinically effective dose of lithium should always be used. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have also been reported in patients on chronic lithium therapy. High serum concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes.

Renal function should be monitored in all patients, not just those with polyuria or polydipsia, e.g with measurement of blood urea, serum creatinine and urinary protein levels, in addition to the routine serum lithium estimations. When kidney function is assessed, routine urinalysis and other tests may be used to evaluate tubular function (e.g. urine specific gravity, osmolality following water deprivation or 24-hour urine volume) and glomerular function. Of note, acute renal failure has been reported rarely with lithium toxicity. Patients should be instructed to report any symptoms of polyuria, polydipsia, nausea or vomiting.

Electroconvulsive therapy

Lithium should be temporarily discontinued before electroconvulsive therapy (ECT) to reduce the risk of delirium, which may occur when the two treatments are co-administered.

Surgery

Lithium should be discontinued 24 hours before any major operation. Provided serum electrolytes are in balance it can generally be restarted soon after the operation and the patient appropriately monitored, including renal function. Complete discontinuation of prophylactic lithium therapy should be discussed between patient, general practitioner and specialist.

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.

Brugada syndrome

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

Encephalopathic syndrome

An encephalopathic syndrome, characterised by weakness, lethargy, fever, tremulousness, confusion, extrapyramidal symptoms and leucocytosis has occurred in a few patients treated with lithium and neuroleptics. In some instances, the syndrome was followed by irreversible brain damage. Because there is a possible

causal relationship between these events and treatment with lithium and neuroleptics, patients receiving combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if symptoms appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome.

Benign intracranial hypertension

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

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.

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 such as QT interval prolongation (e.g. uncorrected hypokalaemia, bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QT interval (see sections 4.5 Interactions with other medicines and other forms of interaction and 4.8 Undesirable effects).

Children

Information regarding the safety and efficacy in children under 12 years of age is not available, therefore lithium therapy is not recommended in this age group.

Priadel is not recommended in adolescents and children (see section 4.2 Dosage and method of administration).

Elderly

Elderly patients are at a greater risk of lithium toxicity. Lithium should be used with care in the elderly, as excretion may be reduced, half-life increased, and signs of toxicity can occur at serum concentrations ordinarily tolerated by younger patients. Elderly patients often require lower dosages to achieve therapeutic serum concentrations

4.5 Interactions with other medicines and other forms of interaction

If one of the following medicines is initiated, regular monitoring of serum lithium levels and for signs of lithium toxicity should be performed during concomitant treatment. Lithium dosage should either be adjusted or concomitant treatment stopped, as appropriate:

Interactions that may increase lithium concentrations:

- Selective Serotonin Re-uptake Inhibitors (SSRIs)
- Metronidazole
- Tetracyclines
- 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.
- Non-steroidal anti-inflammatory drugs (NSAIDs)

- ACE inhibitors
- Thiazide diuretics (may cause a paradoxical anti-diuretic effect resulting in possible water retention and lithium intoxication)
- Spironolactone
- Frusemide
- Angiotensin-II receptor antagonists
- Other medicines affecting electrolyte balance may alter lithium excretion, e.g. steroids

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.

Interactions that may decrease lithium concentrations:

- Xanthines (theophylline, caffeine)
- Sodium bicarbonate and sodium chloride containing products
- Psyllium or ispaghula husk
- Urea
- Mannitol
- Acetazolamide
- Empagliflozin
- Dapagliflozin

Interactions that may cause neurotoxicity:

- Neuroleptics (risperidone, clozapine, phenothiazines, and particularly haloperidol) may lead to, in rare cases, neurotoxicity in the form of confusion, disorientation, lethargy, tremor, extra-pyramidal symptoms and myoclonus. In some instances, the syndrome was followed by irreversible brain damage. Because there is a possible causal relationship between these events and treatment with lithium and neuroleptics, patients receiving combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if symptoms appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome.
- SSRIs, sumatriptan and tricyclic antidepressants have been associated with episodes of neurotoxicity, and may precipitate a serotoninergic syndrome – either event justifies immediate discontinuation of treatment
- Calcium channel blockers may lead to a risk of neurotoxicity in the form of ataxia, confusion and somnolence, reversible after discontinuation of the medicine. Lithium concentrations may be increased or decreased
- Carbamazepine or phenytoin may lead to dizziness, somnolence, confusion and cerebellar symptoms
- Methyldopa
- Lithium can increase serotonin levels which may lead to serotonin syndrome when taken with other medicines that are also serotonergic.
- Caution is advised if lithium is co-administered with drugs that lower the epileptic threshold due to increased risk of convulsions (see section 4.4 Special warnings and precautions for use).

Other interactions:

- Lithium may prolong the effects of neuromuscular blocking agents
- Thioridazine may increase risk of ventricular dysrhythmias
- Iodide and lithium may act synergistically to produce hypothyroidism
- There have also been case reports of lithium interactions with baclofen, cotrimoxazole, acyclovir and prostaglandin-synthetase inhibitors. The clinical significance of these interactions is uncertain.

QT prolongation

Caution is advised if lithium is co-administered with other drugs that prolong the QT interval (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects), 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. The list is not comprehensive.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraception throughout lithium treatment should be considered and a joint decision between prescriber and patient should be made when considering continuation of lithium treatment in pregnancy.

Pregnancy

Category D: Medicines which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The risk of birth defects may be increased when lithium is used during the first trimester. Second trimester detailed ultrasound examination and foetal echocardiography should be considered for women who have been treated with lithium during the first trimester of pregnancy. The newborn may show signs of lithium toxicity.

PRIADEL should not be used during pregnancy, especially during the first trimester, unless considered essential. Women of child-bearing potential should use effective contraceptive methods during treatment with lithium. There is epidemiological evidence that lithium 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.

Cardiac malformations, especially Ebstein abnormality, and other malformations have been reported. Therefore, a prenatal diagnosis such as ultrasound and electrocardiogram examination is strongly recommended. In a meta-analysis of six cohorts of pregnant women and their children[1], the absolute risk of infant cardiac malformations after exposure to lithium during the first trimester was 2.1%, which is similar to the 2.4% absolute risk described in another study[2].

Treatment decisions between the prescriber and patient should be made as early as possible before conception. If a woman taking lithium wishes to become pregnant, consider stopping the medicine gradually over 4 weeks if she is well.

In certain cases where a severe risk to the patient could exist if treatment were stopped, lithium has been continued during pregnancy. Consider stopping lithium and restarting treatment after the first trimester or immediately post-partum. If it is considered essential to maintain treatment during pregnancy, serum lithium levels should be monitored frequently, since renal function changes gradually during pregnancy and suddenly at parturition. Dosage adjustments are required. If lithium is used during organogenesis, foetal echocardiography and level-2 ultrasound should be performed. It is recommended that lithium be discontinued shortly before delivery and recommenced 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.

Breast-feeding

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

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1 Munk-Olsen T et al. The Lancet Psychiatry. 2018 Aug;5(8):664-52
2 Patorno E et al. The New England Journal of Medicine. 2017 Aug 31;377(9):893-4

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.

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 Undesirable effects), patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual sensitivity to lithium and generally occur more frequently and with greater severity at higher concentrations.

The most frequent adverse effects are the initial post-absorptive symptoms, believed to be associated with a rapid rise in serum lithium levels. They include gastrointestinal discomfort with mild nausea and diarrhoea, vertigo, muscle weakness and a dazed feeling and frequently disappear after stabilisation of therapy. Fine tremor of the hands, thirst and polyuria may persist. Weight gain or oedema may present in some patients but should not be treated with diuretics.

The following reactions appear to be related to serum lithium concentrations. Adverse reactions can occur in patients with serum concentrations within the therapeutic range (i.e. below 1.5 mmol/L or lower in the elderly). Adverse effects occurring at therapeutic serum lithium concentrations include anorexia, constipation or diarrhoea, epigastric discomfort, metallic taste, headache, vertigo, fine tremor, polyuria with polydipsia, and oedema.

The frequency at which reactions may occur are: Very common (1/10); common (1/100 to < 1/10; uncommon (1/1,000 to < 1/100); rare (1/10,000 to < 1/1,000; very rare (< 1/10,000); unknown.

Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
General disorders and administration site conditions	Angioedema, oedema, urticaria	Unknown
Cardiac disorders	Bradycardia, Sinus node dysfunction, arrhythmia, QT prolongation, AV block, cardiomyopathy, Brugada syndrome (Unmasking/aggravation)	Unknown
Vascular disorders	Raynaud's phenomena, Hypotension, Peripheral circulatory failure	Unknown
Investigations	ECG changes including T wave changes	Unknown
Skin and subcutaneous tissue disorders	Acne, rash, folliculitis, exacerbation of Psoriasis, papular skin disorders, cutaneous ulcers, lichenoid drug interactions, alopecia, pruritus, Drug reaction with eosinophilia and systemic symptoms (DRESS)	Unknown
Endocrine disorders	Hyperthyroidism, euthyroid goitre, hypothyroidism, hypermagnesaemia, hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia	Unknown
	Hypercalcaemia	Very Common
Metabolism and nutrition disorders	Decreased appetite, dysgeusia, hyperglycaemia, weight gain	Unknown
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, gastritis, salivary hypersecretion, abdominal pain, dry mouth, anorexia	Unknown
Blood and lymphatic disorders	Leukocytosis	Unknown
Eye disorders	Blurred vision, scotoma	Unknown
Nervous system disorders	Myasthenia gravis, dizziness, tremor, fasciculations, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes, extrapyramidal symptoms, syncope, seizures, slurred speech, vertigo, nystagmus, somnolence, stupor, coma, taste distortion, taste impairment, pseudotumour cerebri (benign intracranial hypertension), abnormal reflexes, autonomic dysfunction, myoclonus, impaired consciousness, encephalopathy, cerebellar syndrome, serotonin syndrome, neuroleptic malignant syndrome, memory impairment, peripheral neuropathy	Unknown
Psychiatric disorders	Hallucinations, confusion, delirium	Unknown
Musculoskeletal and connective tissue disorders	Muscle twitching, muscle weakness, rhabdomyolysis	Unknown
Reproductive system and breast disorder	Impotence, sexual dysfunction	Unknown
Renal and urinary disorders	Polydipsia, polyuria, nephrogenic diabetes insipidus, nephrotic syndrome, Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy).	Unknown

Description of selected adverse reactions

Cardiac

Reversible ECG changes e.g. T wave flattening, or inversion, cardiac arrhythmias and EEG changes have been reported.

Endocrine

Hypercalcaemia has been reported in about 10% of patients taking lithium, hypermagnesaemia and hyperparathyroidism have also been reported.

Renal

Polydipsia and/or polyuria and nephrogenic diabetes insipidus, histological renal changes with interstitial fibrosis after long term treatment have been reported (see section 4.4 Special warnings and precautions for use). This is usually reversible on lithium withdrawal.

Long-term treatment with lithium may result in permanent changes in kidney histology, and impairment of renal function.

High serum concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes. Rare cases of nephrotic syndrome have been reported.

Long term use

Long term treatment with lithium may be associated with disturbances of thyroid function, including goitre, hypothyroidism and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine.

Memory impairment may occur during long term use. After a period lasting 3-5 years, patients should be carefully assessed to ensure that benefit persists.

Lithium toxicity

Toxic effects may be expected at serum-lithium concentrations over 1.5 mmol/L, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously (see section 4.4 Special warnings and precautions for use).

Signs of toxicity include increasing diarrhoea, vomiting, anorexia, severe abdominal discomfort, polyuria, muscle weakness, lethargy, ataxia, lack of co-ordination, tinnitus, blurred vision, dry mouth, dysgeusia and impotence/sexual dysfunction, coarse tremor (marked) of the extremities and lower jaw, muscle hyperirritability and twitching, agitation, hyper-reflexia, choreoathetoid movements, dysarthria, disorientation, psychosis, drowsiness, seizures and coma. At higher concentrations, ataxia, tinnitus, blurred vision, giddiness and increasing polyuria are seen.

Serotonin syndrome

Serotonin syndrome is a potentially life-threatening adverse reaction, with is caused by an excess of serotonin (e.g. from overdose or concomitant use of serotonergic drugs), necessitating hospitalisation and even causing death.

Symptoms may include:

- Mental status changes (agitation, confusion, hypomania, eventually coma)
- Neuromuscular abnormalities (myoclonus, tremor, hyperreflexia, rigidity, akathisia)
- Autonomic hyperactivity (hypo or hypertonia, tachycardia, shivering, hyperthermia, diaphoresis)
- Gastrointestinal symptoms (diarrhoea)

Paediatric population

No information available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms

In acute overdosage, vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a latency period and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdosage are reported to be mainly related to the alimentary and nervous systems and include abdominal pain, anorexia, nausea, vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, depression, renal symptoms.

Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

Treatment

Treatment is symptomatic and supportive; recommend closely monitoring vital signs. Activated charcoal is of no value. Whole bowel irrigation has been suggested although there do not appear to be clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured and any electrolyte imbalance corrected, but forced diuresis or diuretics are contraindicated. Appropriate supportive care may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mood-stabilising agent.

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AN01

Mechanism of action

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

Lithium is rapidly absorbed from the gastrointestinal tract. Steady-state lithium levels may not be obtained until 4 to 6 days.

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

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.

Lithium is not metabolised in the liver.

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.

Elimination half-life may be increased in elderly patients due to age-related disease in renal function and also in patients with renal impairment (see section 4.2 Dose and method of administration, and section 4.4 Special warnings and precautions for use.)

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the data sheet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia

Glyceryl palmito-stearate

Magnesium stearate

Maize starch

Mannitol

Sodium laurilsulfate

Sodium starch glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C. Dispense in airtight containers.

6.5 Nature and contents of container

Blister packs of 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

31 December 1969.

10. DATE OF REVISION OF THE TEXT

23 August 2024

Summary Table of Changes

Section Changed	Summary of New Information
4.1	Editorial change.
4.2	Reformatting of text to improve clarity of the current information. Additional information about monitoring, withdrawal and use in renal impairment.
4.3	Addition of 'untreated hypothyroidism' and 'Brugada Syndrome or family history of Brugada Syndrome' as contraindications.
4.4	Reformatting of text to improve clarity of the current information. Additional information on pre-treatment and on treatment monitoring. Additional information on electroconvulsive therapy, surgery, Brugada syndrome, Encephalopathic syndrome, Benign intracranial hypertension, convulsions, QT prolongation, and children.
4.5	Additional information relating to lithium interactions.
4.6	Additional statement on women of childbearing potential.

4.8	Adverse reactions moved into table format. Additional adverse reactions and information included.