

## NEW ZEALAND DATA SHEET

### 1. PRIADEL MODIFIED 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.

### 3. PHARMACEUTICAL FORM

Modified 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. Lithium may also be tried in the treatment of some patients with recurrent bipolar depression, for which treatment with other antidepressants has been unsuccessful.
3. Prophylactic treatment of recurrent affective disorders.

#### 4.2 Dose and method of administration

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 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. 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. 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.

2. 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.
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. In practice, the blood sample should be taken between 12 and 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)**

	<b>At 12 hours</b>	<b>At 24 hours</b>
Once daily dosage	0.7-1.0	0.5-0.8
Twice daily dosage	0.5-0.8	

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 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.
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 Special warnings and precautions for use.)

#### **Treatment of acute mania, hypomania and recurrent bipolar depression**

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.

#### **Prophylactic treatment of recurrent affective disorders**

It is recommended that the described treatment schedule is followed.

## Special populations

### 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. 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.

## 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

## 4.4 Special warnings and precautions for use

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. It is important to ensure that renal function is normal – if necessary a creatinine clearance test or other renal function test should be performed. 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. Renal function, cardiac function, thyroid and parathyroid function should be reassessed periodically. Care should be taken in the presence of Encephalopathic syndrome or intercurrent infection.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long term lithium therapy (see Lithium toxicity, below). Patients should also be warned to report if polyuria or polydipsia develop. Episodes of nausea and vomiting or other conditions leading to salt/water depletion (including severe dieting) should also be reported. Elderly patients are particularly liable to lithium toxicity.

Caution should be exercised to ensure that diet and fluid intake are normal, thus maintaining 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 infections may alter fluid balance and thus affect serum lithium levels. Treatment should be discontinued during any intercurrent infection and should only be reinstated after the patient's physical health has returned to normal.

### 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 impending lithium intoxication, such as:

1. Gastro-intestinal: increasing anorexia, 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, coarse tremor and muscle twitching.

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

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

### **Monitoring requirements**

As described under Dosage and Administration, monitoring of lithium levels should include pre-treatment testing and ongoing clinical and laboratory evaluations. Monitoring frequency should be increased when the dosage is changed, if the patient is unwell, or if signs of lithium toxicity develop.

### **Renal impairment/nephrotoxicity**

Up to one third of patients on lithium may develop nephrogenic diabetes insipidus, characterised by polyuria, polydipsia and a urinary output of up to three litres per day. This is usually due to lithium blocking the effect of ADH and is reversible on lithium withdrawal. However, long term treatment with lithium may also 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. The minimum clinically effective dose of lithium should always be used. 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. Patients should be instructed to report any symptoms of polyuria, polydipsia, nausea or vomiting.

## **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 Interaction 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
- 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

#### **Interactions that may decrease lithium concentrations:**

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

#### **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
- SSRIs, sumatriptan and tricyclic antidepressants have been associated with episodes of neurotoxicity, and may precipitate a serotonergic 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

### 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.

## 4.6 Fertility, pregnancy and lactation

### 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.

### 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<sup>1</sup>, 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<sup>2</sup>.

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

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1 Munk-Olsen T et al. The Lancet Psychiatry. 2018 Aug;5(8):664-52

2 Paterno E et al. The New England Journal of Medicine. 2017 Aug 31;377(9):893-4

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.

### **Breastfeeding**

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). 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.

## **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**

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol/L.

Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur initially, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist. Weight gain or oedema may present in some patients but should not be treated with diuretics.

Hypercalcaemia has been reported in about 10% of patients taking lithium, hypermagnesaemia and hyperparathyroidism have also been reported. Skin conditions including acne, psoriasis, generalised pustular psoriasis, rashes and leg ulcers have occasionally been reported as being aggravated by lithium treatment.

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.

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).

*Body as a whole:* oedema

*Cardiovascular:* cardiac arrhythmia, hypotension, ECG changes including nonspecific T wave changes, oedema, Raynaud's phenomena, peripheral circulatory collapse, bradycardia, sinus node dysfunction.

*Dermatologic:* alopecia, acne, folliculitis, pruritus, psoriasis exacerbation, rash.

*Endocrine:* euthyroid goitre, hypothyroidism, rare cases of hyperthyroidism, hyperglycaemia, hypercalcaemia, hyperparathyroidism, weight gain.

*Gastrointestinal:* anorexia, nausea, vomiting, diarrhoea, gastritis, excessive salivation, abdominal pain.

*Haematological:* leucocytosis.

*Hypersensitivity:* angioedema.

*Neuromuscular/CNS:* tremor, fasciculations, twitching clonic movements of extremities, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes, extrapyramidal symptoms, syncope, seizures, slurred speech, dizziness, vertigo, nystagmus, somnolence, stupor, coma, hallucinations, taste distortion, taste impairment, scotomata, pseudotumour cerebri, autonomic effects including blurred vision, dry mouth, dysgeusia and impotence/sexual dysfunction. Myasthenia gravis has been observed rarely.

*Renal:* symptoms of nephrogenic diabetes insipidus.

### **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 to <https://nzphvc.otago.ac.nz/reporting/>.

## **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 764 766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Mood-stabilising agent.

Pharmacotherapeutic group: Antipsychotics – ATC code: N05AN01.

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 for disposal. Any used 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

4 April 2019

## SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6 Fertility, pregnancy and lactation	Fertility heading and animal data included. Information on use in pregnancy updated, in line with recommendations from the Medicines Adverse Reactions Committee meeting, 6 December 2018. Additional information on breastfeeding included.