

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Priadel 520mg/5ml Liquid.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

520mg lithium citrate equivalent to 204mg lithium carbonate per 5ml.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Syrup.

Clear, colourless, pineapple flavoured, sugar free syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. In the management of acute manic or hypomanic episodes.
2. In the management of episodes of recurrent depressive disorders where treatment with other antidepressants has been unsuccessful.
3. In the prophylaxis against bipolar affective disorders.
4. 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.

As a general rule, the following dosing schedule is recommended. Please refer also to the specific recommendations for the different indications as listed below:

1. In patients of average weight (70kg) an initial daily dose of 10-30ml Priadel Liquid (equivalent to 408-1224mg lithium carbonate) should be given in divided doses, ideally twice a day. When changing between lithium preparations serum lithium levels should first be checked, then Priadel Liquid 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 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. Optimal maintenance serum levels may vary from patient to patient.
3. Blood samples should be taken 12 or 24 hours after the previous dose of lithium, just before the next dose is due, to measure the serum lithium level at its trough.

The objective is to adjust the Priadel dose so as to maintain the "Target" serum lithium

concentrations at 12 and 24 hours shown in the table below.

| “Target” serum lithium concentration (mmol/l) | At 12 hours At 24 hours | |
|---|------------------------------|-----------|
| | Once daily dosage | 0.7 – 1.0 |
| Twice daily dosage | 0.5 – 0.8 | |

Priadel Liquid is supplied with a 2.5/5ml double ended spoon to provide adjustments equivalent to 102mg and 204mg lithium carbonate respectively. Serum lithium levels should be monitored weekly until stabilisation is achieved. The serum level should not exceed 1.5 mmol/l.

The liquid 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.

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 measurements 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 therapy with Priadel Liquid it 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 with Priadel Liquid, treatment is likely to be long term. Careful clinical appraisal of the patient should be exercised throughout medication (see Precautions).

7. If lithium is to be discontinued, particularly in cases of high doses, the dose should be reduced gradually.

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. The dosage needed may vary from patient to patient. As a general rule, serum lithium levels should be maintained within the range of 0.5 to 1.0 mmol/l, and should not exceed 1.5 mmol/l. Optimal maintenance serum lithium levels may vary from patient to patient.

Treatment of acute manic or hypomanic episodes and recurrent depressive disorders: It is likely that a higher than normal Priadel Liquid intake may be necessary during an acute phase. 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.

Elderly:

Elderly patients or those below 50kg in weight, often require lower lithium dosage to achieve therapeutic serum lithium levels. Starting doses of 204mg to 408mg are recommended taken twice daily. Dosage increments of 204 to 408mg every 3 to 5 days are usual. Total daily doses of 816 to 1836mg 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 612 to 1224 mg/day.

Children and adolescents:

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).

4.3 Contra-indications

- Hypersensitivity to lithium or to any of the excipients.
- Cardiac disease.
- Cardiac insufficiency.
- Severe renal impairment.
- Untreated hypothyroidism.
- Breast-feeding.
- Patients with low body sodium levels, including for example dehydrated patients or those on low sodium diets.
- Addison's disease.
- Brugada syndrome or family history of Brugada syndrome.

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). They should be warned of the urgency of immediate action should these symptoms appear, and also of the need to maintain a constant and adequate salt and water intake. Treatment should be discontinued immediately on the first signs of toxicity (see Section 4.9).

• **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**

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).

The possibility of hypothyroidism and renal dysfunction arising during prolonged treatment should be borne in mind and periodic assessments made.

Patients should 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.

- **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. Drugs likely to upset electrolyte balance such as diuretics should also be reported. Indeed, sodium depletion increases the lithium plasma concentration (due to competitive reabsorption at the renal level). In these cases, lithium dosage should be closely monitored and reduction of dosage may be 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 infections 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 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 and 4.8).

- **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 should not be administered to patients with 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.

- **Elderly patients**

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 disease in renal function (see Sections 4.2 and 5.2).

- **Children**

The use in children is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions which increase lithium concentrations:

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.

- Metronidazole may reduce lithium renal clearance.
- Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase (COX) 2 inhibitors (monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Angiotensin II receptor antagonists.

- Diuretics (thiazides show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication). If a thiazide diuretic has to be prescribed for a lithium-treated patient, lithium dosage should first be reduced and the patient re-stabilised with frequent monitoring. Similar precautions should be exercised on diuretic withdrawal. 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.
- Tetracyclines.

Interactions which decrease serum lithium concentrations:

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:

- Xanthines (theophylline, caffeine).
- Sodium bicarbonate containing products.
- Diuretics (osmotic and carbonic anhydrase inhibitors).
- Urea.

Interactions causing neurotoxicity:

Co-administration of the following drugs may increase the risk of neurotoxicity:

- Antipsychotics (particularly haloperidol at higher dosages), flupentixol, diazepam, thioridazine, fluphenazine, chlorpromazine and clozapine may lead in rare cases to severe 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. Discontinuation of both drugs is recommended at the first signs of neurotoxicity.
- Methyldopa.
- Triptan derivatives and/or serotonergic antidepressants such as Selective Serotonin Re-uptake Inhibitors (e.g. fluvoxamine and fluoxetine) as this combination may precipitate a serotoninergic syndrome*, which justifies immediate discontinuation of treatment.
- Calcium channel blockers may lead to neurotoxicity with symptoms such as ataxia, confusion and somnolence. Lithium concentrations may be increased.
- Carbamazepine may lead to dizziness, somnolence, confusion and cerebellar symptoms such as ataxia.

Other

Caution is advised if lithium is co-administered with other drugs that prolong the QT interval (see Sections 4.4 and 4.8), 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.

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. The list is not comprehensive

Lithium may prolong the effects of neuromuscular blocking agents. There have been reports of interaction between lithium and phenytoin, indomethacin and other prostaglandin-synthetase inhibitors.

***Serotonin syndrome**

Serotonin syndrome is a potentially life-threatening adverse reaction, which 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)

Strict adherence to the recommended doses is an essential factor for the prevention of the occurrence of this syndrome.

4.6 Use during pregnancy and lactation

4.6.1 Pregnancy

Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. There is epidemiological evidence that it may be harmful to the foetus in human pregnancy. Lithium crosses the placental barrier. In animal studies lithium has been reported to interfere with fertility, gestation and foetal development. Cardiac especially Ebstein anomaly, and other malformations have been reported. Therefore, a pre-natal diagnosis such as ultrasound and electrocardiogram examination is strongly recommended. In certain cases where a severe risk to the patient could exist if treatment were stopped, lithium has been continued during pregnancy.

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

Neonates may show signs of lithium toxicity 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.

4.6.2 Women of child-bearing potential

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

4.6.3 Lactation

Lithium is secreted in breast milk and there have been case reports of neonates showing signs of lithium toxicity (see Section 4.6.1). 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.

4.7 Effects on ability to drive and use machines

Lithium may cause disturbances of the CNS. 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 operating machinery.

4.8 Undesirable effects

Side effects are usually related to serum lithium concentration and are less common in patients with plasma lithium concentrations 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 and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine.

Hypercalcaemia, hypermagnesemia, hyperparathyroidism have been reported.

- Metabolism and nutrition disorders:
Weight increase, hyperglycaemia.
- Psychiatric disorders:
Confusion.
- Nervous system disorders:
Ataxia, hyperactive deep tendon reflexes, slurred speech, dizziness, nystagmus, stupor, coma, myasthenia gravis, giddiness, dazed feeling, memory impairment.

Tremor, especially fine hand tremors, vertigo, dysarthria, impaired consciousness, myoclonus, abnormal reflexes, convulsions (see Sections

4.4 and 4.5), benign intracranial hypertension (see Section 4.4), extrapyramidal disorders.

- Cardiac disorders:
Cardiac arrhythmia, mainly bradycardia, sinus node dysfunction, peripheral circulatory collapse, hypotension, ECG changes such as reversible flattening or inversion of T-waves and QT prolongation (see Sections 4.4 and 4.5), AV block, cardiomyopathy.
- Gastrointestinal disorders:
Abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, salivary hypersecretion, dry mouth, anorexia.
- Skin and subcutaneous tissue disorders:
Folliculitis, pruritus, papular skin disorders, acne or acneform eruptions, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers.
- Musculoskeletal and connective tissue disorders:
Muscle weakness.
- Renal and urinary disorders:
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). 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.

- General disorders and administration site conditions:
Peripheral oedema.
- Reproductive:
Sexual dysfunction.
- Senses:
Dysgeusia, blurred vision, scotomata.

If any of the above symptoms appear, treatment should be stopped immediately and arrangements made for serum lithium measurement.

4.9 Overdose

In patients with a raised lithium concentration, the risk of toxicity is greater in those with the following underlying medical conditions: hypertension, diabetes,

congestive heart failure, chronic renal failure, schizophrenia, Addison's disease.

Acute

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

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

Chronic

Lithium toxicity can also occur in chronic accumulation for the following reasons: Acute or chronic overdosage; dehydration e.g. due to intercurrent illness, deteriorating renal function, drug interactions, most commonly involving a thiazide diuretic or a non-steroidal anti-inflammatory drug (NSAID).

Symptoms

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

Symptoms of lithium intoxication include:

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

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

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

Others

Gastrointestinal disorders: increasing anorexia and vomiting.

Nervous system disorders: lack of coordination, lethargy, giddiness, ataxia, nystagmus, tinnitus, dysarthria, coarse tremor, twitching, myoclonus, extrapyramidal disorders.

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.

Diuretics should not be used (see Section 4.5). All patients should be observed

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

Consider gastric lavage for non-sustained-release preparations if more than 4 g has been ingested by an adult within 1 hour or definite ingestion of a significant amount by a child. Slow-release tablets do not disintegrate in the stomach and most are too large to pass up a lavage tube. Gut decontamination is not useful for chronic accumulation. Activated charcoal does not adsorb lithium.

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.

In cases of acute or chronic overdose or in cases of chronic lithium toxicity if the lithium concentration is >4.0 mmol/l, discuss with your local poisons service.

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

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.

The mode of action of lithium is still not fully understood. 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 has a half-life of about 24 hours although this increases to about 36 hours in the elderly due to a progressive decrease in renal lithium clearance with age. Lithium is 95% eliminated in the urine. Time to peak serum level for an immediate release product, such as Priadel Liquid, is about 1.5 hours and complete bioavailability would be expected.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients include:

Ethanol, xanthan gum, saccharin sodium, sorbic acid, citric acid, pineapple flavour, purified water.

6.2 Major incompatibilities

Dilution of Priadel Liquid is not recommended.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Store at or below 25°C. Protect from direct sunlight.

6.5 Nature and contents of container

Priadel Liquid is supplied in an amber glass bottle fitted with a one-piece polypropylene screw cap. Packs are available in 150ml and 300ml volumes.

Priadel Liquid is supplied with a 2.5/5ml double ended spoon.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 MARKETING AUTHORISATION NUMBER

04425/0354

9 DATE OF THE FIRST AUTHORISATION OR RENEWAL

26 March 2009

10 DATE OF REVISION OF THE TEXT

10 March 2011

Legal category

POM