IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/156/003
Case No: 2027972

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA0077/151/001.

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Priadel Syrup

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/11/2007** until **31/07/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Priadel Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lithium citrate 520 mg equivalent to 200 mg lithium carbonate per 5 ml.

For excipients, see 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

A simple treatment schedule has been evolved which except for some minor variations should be followed whether using Priadel Liquid 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 (70kg) an initial daily dose of 10-30ml Priadel Liquid (equivalent to 400-1200mg 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 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 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 estimation of serum lithium level.

3. The objective is to adjust the Priadel Liquid dose so as to maintain the serum lithium level permanently within the diurnal range of 0.5-1.5mmol/l. In practice, the blood sample should be taken 12 hours after the previous dose of Priadel Liquid. “Target” serum lithium concentrations at 12 hours should be 0.5-0.8mmol/l.

Priadel Liquid is supplied with a 2.5/5ml double ended spoon to provide dosage adjustments equivalent to 100mg and 200mg lithium carbonate respectively. 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 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 to therapy with Priadel Liquid, treatment is likely to be long term. Careful clinical appraisal of the patient should be exercised throughout medication (see Precautions).

Prophylactic treatment of bipolar affective disorders and control of aggressive behaviour or intentional self-harm*:* It is recommended that the described treatment schedule is followed.

Treatment of acute mania, 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 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 Liquid and re-stabilise serum lithium levels.

Use in mentally handicapped patients who appear particularly susceptible to lithium neurotoxicity, levels should not be allowed to exceed 1mmol/litre.

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

Children and adolescents: Not recommended.

4.3 Contraindications

- Hypersensitivity to lithium or to any of the excipients.
- Cardiac failure.
- Clinically significant renal impairment.
- Addison's disease.
- Untreated hypothyroidism.
- Breast-feeding.

4.4 Special warnings and precautions for use

- When considering therapy with Priadel Liquid, it is necessary to ascertain whether patients are receiving lithium in any other form. If so, check serum levels before proceeding.
- <u>Before beginning a lithium treatment:</u>
  - it is important to ensure that renal function is normal.
  - cardiac function should be assessed and caution exercised in patients with cardiovascular disease which may predispose to prolongation of the QT interval.
  - Avoid concomitant prescription of other antipsychotics.
  - thyroid function should be evaluated. Patients should be euthyroid before initiation of lithium therapy.
- Renal, cardiac and thyroid functions should be re-assessed periodically.
- Adjustment of dosage depends closely on levels of serum lithium and the assays should be carried out as necessary (after achievement of steady state) to permit adequate control and prevent toxicity.

- Patients on lithium therapy should be kept under regular surveillance with particular attention to the appearance of signs of toxicity. The minimum clinically effective dose should always be used.
- Clear instructions regarding the symptoms of impending toxicity should be given by the physician to patients receiving long term lithium therapy (see 4.9 Overdose – Toxic effects).
  Patients should also be warned to report if polyuria or polydipsia develops. Episodes of nausea, vomiting, diarrhoea, excessive sweating and/or other conditions leading to salt/water depletion (including severe dieting) should also be reported. In those cases, lithium dosage should be closely monitored.
- 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 should be discontinued during any intercurrent infection and should only be reinstituted after the patient's physical health has returned to normal.
- Use in patients requiring a low sodium intake is not normally recommended.
- Elderly patients are particularly liable to lithium toxicity. They may exhibit adverse reactions at serum levels ordinarily tolerated by younger patients.

4.5 Interaction with other medicinal products and other forms of interaction

Serum lithium concentration may be increased if one of the following drugs is initiated – lithium dosage should either be adjusted or concomitant treatment stopped, as appropriate:

- **Thiazide diuretics** may cause reduced lithium clearance, leading to 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.
- **Other drugs affecting electrolyte balance, e.g. steroids**, may alter lithium excretion and should therefore be avoided.
- **Non-steroidal anti-inflammatory drugs (NSAIDs)** can increase serum lithium concentrations, possibly resulting in lithium toxicity. Serum lithium concentrations should be monitored more frequently if NSAID therapy is initiated or discontinued.
- Angiotensin-converting enzyme inhibitors.
- Metronidazole may reduce lithium renal tolerance.
- **Tetracyclines.**
- **Methyldopa.**

Serum lithium concentration may be **decreased** due to lithium clearance increase in case of concomitant administration of one of the following drugs:

- **Osmotic diuretics** and **carbonic anhydrase inhibitors.**
- **Xanthine** (theophylline, caffeine).
- **Sodium bicarbonate.**

Other interactions:

- **Triptan derivatives** and/or **serotinergic antidepressants** may result in occurrence of serotonininergic syndrome, which 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 drug. Lithium concentrations may be increased.
- **Psychotropic/neuroleptic drugs** such as haloperidol, flupentixol, phenytoin, diazepam, thioridazine, fluphenazine, chlorpromazine and clozapine may lead in rare cases to neurotoxicity in the form of confusion, disorientation, lethargy, tremor, extra-pyramidal symptoms and myoclonies with sometimes a rapid increase of serum lithium concentration.
- **Carbamazepine** may lead to dizziness, somnolence, confusion and cerebellar symptoms.
- The risk of prolongation of the QT interval is increased when antipsychotics are prescribed in association with a medication likely to product pronounced bradycardia (< 55bpm), electrolyte imbalance, in particular hypokalaemia, decreased intracardiac conduction, or to prolong the QTc interval.

4.6 Pregnancy and lactation

4.6.1. Pregnancy

Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. It may be harmful to the foetus in human pregnancy. An increase in cardiac and other abnormalities, especially Ebstein anomaly, are reported. Therefore, a pre-natal diagnosis such as ultrasound examination is strongly recommended.

If it is considered essential to maintain lithium treatment during pregnancy, serum lithium levels should be closely monitored since renal function changes gradually during pregnancy and suddenly at parturition. Dosage adjustments are required. It is recommended that lithium be discontinued shortly before delivery and reinitiated a few days *post-partum*.
Neonates may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Neonates born with low serum lithium concentrations may have a flaccid appearance that returns to normal without any treatment.

4.6.2. Women of child-bearing potential

It is advisable that women treated with lithium should adopt adequate contraceptive methods. In case of a planned pregnancy, it is strongly recommended to discontinue lithium therapy.

4.6.3. Lactation

Lithium is secreted in breast milk. Therefore, bottle-feeding is recommended (see section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

There are no data available on the effect of Priadel on the ability to drive. Considering the pattern of side effects, the possibility that Priadel may negatively influence reaction-time should be taken into account.

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.

Dermatology: acne, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers.

Musculoskeletal: muscle weakness.

Central nervous system: tremor especially fine hand tremors, vertigo, speech disorder, impaired consciousness, myoclony and abnormal reflex have been reported. Memory impairment may occur during long term use.

Gastrointestinal: abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, salivary hypersecretion, dry mouth.

Endocrine: long term adverse effects may include thyroid function disturbances such as euthyroid goitre and/or hypothyroidism. Rarely hyperthyoidism may also occur. Lithium-induced hypothyroidism may be managed successfully with concurrent levothyroxine. Hypercalcaemia, hypermagnesaemia, hyperparathyroidism have been reported.

Cardiovascular: QT prolongation and ventricular arrhythmias such as torsades de points, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest and sudden death. Other cardiac arrhythmia mainly bradycardia, sinus node dysfunction, ECG changes such as reversible flattening or inversion of T-waves. Cardiomyopathy.

Metabolic and Nutritional: weight increase.

Haematological: leucocytosis.

Renal: polydipsia and/or polyuria, diabetes insipidus. 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.

In patients who develop polyuria and/or polydipsia, renal function should be monitored, e.g. with measurement of blood urea, serum creatinine and urinary protein levels in addition to the routine serum lithium assessment.

Rare cases of nephrotic syndrome.

Psychiatric: confusion.

General disorders: peripheral oedema.

4.9 Overdose

Toxic effects are indicative of impending lithium intoxication and fall into three groups:

- Gastrointestinal: increasing anorexia, diarrhoea and vomiting.
- Central nervous system: muscle weakness, lack of coordination, drowsiness or lethargy progressing to giddiness with ataxia, nystagmus, tinnitus, blurred vision, dysarthria, coarse tremor, muscle weakness and twitching and myoclonia.
- Other: ECG changes (flat or inverted T waves, QT prolongation), 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, seizures, coma and death. There is no specific antidote to lithium poisoning. In the event of accumulation, lithium should be stopped and serum assessment should be carried out every six hours.
Under no circumstances should a diuretic be used. Osmotic diuresis (mannitol or urea infusion) or alkalinisation of the urine (sodium lactate or sodium bicarbonate) should be initiated.
Peritoneal or haemodialysis should be instituted promptly:

- if the serum lithium level is over 4.0 mmol/L,
- if there is a deterioration in the patient's condition,
- or if the serum lithium concentration is not falling at a rate corresponding to a half-life of under 30 hours.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Xanthan gum
Saccharin sodium
Sorbic acid
Citric acid
Pineapple flavour
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle in the outer carton.

6.5 Nature and contents of container

Amber glass bottle fitted with a one-piece polypropylene screw cap. Packs are available in 150 ml and 300 ml bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Dilution of Priadel Syrup is not recommended. There are no special precautions for handling.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 540/156/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 August 1991

Date of last renewal: 01 August 2004

10 DATE OF REVISION OF THE TEXT

November 2007