TJ/15

M E D I C I N E S A C T 1 9 6 8

Product Licence No. PL 0357/5000R

SCHEDULE

Part 1 - PARTICULARS OF THE PRODUCTS TO WHICH THE LICENCE RELATES

1.	Name of Product:	PRIADEL
2.	Pharmaceutical form:	Tablet.
3.	Active constituents:	Lithium Carbonate pH Eur 400mg/tablet.
4.	Uses:	a) Treatment of mania and hypomania b) Lithium may also be tried in the treatment of some patients with re-current bipolar depression, where treatment with other anti-depressants has been unsuccessful. c) Prophylactic treatment of recurrent affective disorders.
5.	Recommended dose and dosage schedule:	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 (400-1200 mg) of Priadel may be given as a single daily dose in the morning or on retiring. Alternatively, the dose may be divided and given morning and evening. The tablets should not be crushed, 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 levels.

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5. Recommended dose and dosage schedule: (continued)

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/1. 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 below.

	"Target" serum lithium concentration (mmol/1)	
	At 12 hours	At 24 Hours
Once daily dosage	0.7-1.0	0.5-0.8
Twice daily dosage	0.5-0.8	

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

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5. Recommended dose and dosage schedule: (continued)

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 Precautions).

Prophylactic treatment of recurrent affective disorders

It is recommended that the described treatment schedule is followed.

Treatment of acute mania, hypomania and re-current 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.

Use in elderly

In elderly patients or those below 50 kg in weight, it is recommended that the starting dose be 1 tablet (400 mg). Elderly patients may be more sensitive to undesirable effects of lithium, and also may 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.

Use in children and adolescents: not recommended.

6. Contra-indications, Precautions and Warnings:

CONTRAINDICATIONS

Renal insufficiency, cardiovascular insufficiency, Addison's disease and untreated hypothyroidism are all contraindications to lithium therapy.

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6. Contra-indications, Precautions and Warnings: (continued)

USE IN PREGNANCY

There is epidemiological evidence that lithium may be harmful to the fetus in human pregnancy.

Total no. "lithium babies" reported	Malformed infants	Ebstein's anomaly and other major cardiovascular malformations
225	25 (11%)	18 (8%)

It is strongly recommended that lithium be discontinued before a planned pregnancy. If it is considered essential to maintain Priadel treatment during pregnancy, serum lithium levels should be closely monitored since renal function changes gradually during pregnancy and suddenly at parturition requiring dosage adjustments. Babies may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Babies born with low serum lithium concentrations may have a flaccid appearance which returns to normal without any treatment. It is recommended that lithium be discontinued shortly before delivery and recommenced a few days post partum.Lithium is secreted in breast milk,therefore bottle feeding is recommended.

PRECAUTIONS

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 and thyroid function should be assessed before commencing lithium treatment. Patients should be euthyroid before the initiation of lithium therapy. Renal function, cardiac function and thyroid function should be reassessed periodically.

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Part 1 - PARTICULARS OF THE PRODUCTS TO WHICH THE LICENCE RELATES

6. Contra-indications, Precautions and Warnings: (continued)

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long term lithium therapy (see Warnings and Adverse Effects). 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 re-instituted when the patient's physical health has returned to normal.

WARNINGS AND ADVERSE EFFECTS

Side effects

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol/1.

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 be present in some patients and should not be treated with diuretics.

Hypercalcaemia, hypermagnesaemia and hyperparathyroidism have been reported. Skin conditions including acne, psoriasis, generalised pustular psoriasis, rashes and leg ulcers have occasionally been reported

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6. Contra-indications, Precautions and Warnings: (continued)

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.

Nephrotoxicity

Up to one third of patients on lithium may develop polyuria with 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. In patients who develop polyuria 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 estimations.

After a period lasting 3-5 years, patients should be carefully assessed to ensure that benefit persists.

Toxic effects

Such effects are indicative of impending lithium intoxication and they fall into

a) Gastro-intestinal: increasing anorexia, diarrhoea and vomiting.

b) Central nervous system: muscle weakness, lack of co-ordination,

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6.	Contra-indications, Precautions and Warnings: (continued)	drowsiness or lethargy progressing to giddiness with ataxia, tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching. At blood level above 2-3 mmol/1 there may be a large output of dilute urine with increasing disorientation, seizures, coma and death. Patients should be instructed to stop taking their tablets if toxic symptoms appear, and to report immediately for a serum lithium estimation.
7.	Legal Category:	PRESCRIPTION ONLY MEDICINE
8.	Method of retail sale or supply:	Through wholesalers, hospitals dispensing doctors and retail pharmacies.
9.a.	Manufacturer of dosage form:	Arthur H Cox & Co Ltd Whiddon Valley Barnstaple Devon EX32 8NS

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Part 2 – FURTHER PROVISIONS SUBJECT TO WHICH THE LICENCE HAS BEEN GRANTED

1. All the provisions of Part I of Schedule 1 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No 972) as amended by the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1972 (SI 1972 No 1226), the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1974 (SI 1974 No 1523) and the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977 (SI 1977 No 1039) shall apply.

2. Leaflets issued with proprietary medicinal products shall comply with the requirements of the Medicines (Leaflets) Regulations 1977 (SI 1977 No 1058). Labels of medicinal products shall comply with the Medicines (Labelling) Regulations 1976 (SI 1976 No 1726) as amended by the Medicines (Labelling) Amendment Regulations 1977 (SI 1977 No 996).

3. The product(s) shall not be recommended to be used for any purposes other than those specified in Part 1 of this Schedule as Uses.

4. The specification of the constituent and of the finished product shall be in accordance with the information contained in the application for this product licence.

5. The product shall be manufactured by the person named in Part I of the Schedule to this licence or by any other person who is licensed to manufacture products of that description in the United Kingdom.