Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Piportil Depot 5% w/v Injection (1 ml Ampoule)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pipotiazine Palmitate 5% w/v (50 mg/ml).
Each 1ml ampoule contains 50 mg Pipotiazine palmitate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
A bright or slightly dim yellow coloured sterile liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of psychotic disorders, particularly for maintenance therapy in patients with chronic schizophrenia.

4.2 Posology and method of administration

Intramuscular injection.

Adults only:

The usual initial dose is 25mg. Subsequent doses should be increased by increments of 25mg or 50mg monthly until a satisfactory response is obtained. The usual dosage is 50 to 100mg once every four weeks but doses of up to 200mg every four weeks may be needed.

The Elderly:

The usual initial dosage is 5 to 10 mg with subsequent slow increments as necessary.

4.3 Contraindications

1. Use in patients hypersensitive to the active ingredient, or other phenothiazines.

2. Use in patients with marked cerebral atherosclerosis or coronary artery or cardiac insufficiency, in coma, or renal or hepatic failure.

4.4 Special warnings and precautions for use

Phenothiazines should only be used with great caution in patients with a history of jaundice or with existent liver dysfunction or blood dyscrasias, epilepsy or myasthenia gravis.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular

attention to potential for inducing eye changes, effects on haemopoiesis, liver dysfunction, myocardial conduction effects, particularly if other concurrently administered drugs also have potential effects on these systems.

Prolonged administration of any phenothiazine may result in persistent or tardive dyskinesias, particularly in the elderly. Prolonged administration of phenothiazines has in a few cases been associated with the development of Tardive Dyskinesia, a syndrome characterised by involuntary dyskinetic movements. Although most usually associated where there is high total cumulative dosing, a few cases have been reported after only small doses have been given or even after therapy has been stopped. Fine vermicular movements of the tongue are reported to be an early sign and their appearance is an indication that treatment should be discontinued. In most instances the syndrome will resolve or not progress. Other groups particularly at risk include the elderly and females.

As with all medications, treatment should be maintained at the lowest clinically effective dose and only for as long as the patient's condition requires.

Phenothiazine derivatives may cause a rise in serum prolactin concentrations and should be avoided in patients suffering from mammary tumours or in those who have undergone mastectomy operations. They may also diminish further thyroid dysfunction.

The anticholinergic activity of the active ingredient requires that it be used with caution in patients with potential or existing narrow angle glaucoma, phaeochromocytoma, thyrotoxicosis, prostatic hypertrophy, respiratory insufficiency or those exposed to very cold or hot ambient temperatures.

Phenothiazines should only be used with great caution in patients with coronary insufficiency or cardiovascular disorders which may predispose to prolongation of the QT interval.

Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsades de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e. drug induced) QT prolongation. (see section 4.5 Interactions with other medicinal products and other forms of interaction). If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (See Section 4.8 Undesirable Effects).

Except in emergencies, it is recommended that an ECG be performed as part of the initial evaluation of the patients due to receive treatment with a neuroleptic agent.

All patients should be advised that if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

Neuroleptic malignant syndrome: The syndrome may occur with the use of any neuroleptic agent. Symptoms include clouding of consciousness, rigidity and other extrapyramidal effects, and autonomic dysfunction, most importantly hyperpyrexia. Treatment involves the immediate cessation of neuroleptic therapy and symptomatic management as appropriate.

Avoid concomitant prescription of other antipsychotics.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:

- Dopaminergic agonists (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole) except in patients with Parkinson's disease: mutual antagonism between dopaminergic agonists and neuroleptics. Patients presenting with neuroleptic-induced extrapyramidal syndromes should not be treated with dopaminergic agonists; anticholinergic agents should be used instead.

Inadvisable combinations:

- Alcohol: potentiation of sedative effects induced by neuroleptic drugs. Impaired alertness may make driving vehicles and using machines dangerous. Patients should not consume alcoholic beverages or take medicines containing alcohol.
- Levodopa: mutual antagonism between levodopa and neuroleptics. In patients with Parkinson's disease, minimum effective doses of each of these drugs should be used.
- Dopaminergic agonists (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole) in patients with Parkinson's disease: mutual antagonism between dopaminergic agonists and neuroleptics. Dopaminergic agonists may cause or exacerbate psychotic disorders. Should neuroleptic therapy be necessary in patients with Parkinson's disease treated with dopaminergic agonists, the dose of dopaminergic agents should be reduced gradually until discontinuation (abrupt discontinuation of this treatment could cause 'neuroleptic malignant syndrome').

Concomitant drugs which could induce prolongation of the QT interval or torsades de pointes (see section 4.4 Special Warnings and Precautions for Use):

- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce electrolyte imbalance, in particular those causing hypokalaemia (such as hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides). Electrolyte imbalance should be corrected.
- Class Ia antiarrhythmic agents such as quinidine, disopyramide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.

Other medications such as pimozide, sultopride, haloperidol; imipramine antidepressants; lithium, bepridil, cisapride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

Combination requiring precautions for use:

- Topical agents for gastrointestinal use (salts, magnesium, aluminium and calcium oxides and hydroxides): decreased gastrointestinal absorption of phenothiazine neuroleptics. Allow for an interval between administration of topical gastrointestinal agents and phenothiazine neuroleptic agents (more than 2 hours apart, if possible).

Combinations to be taken into consideration:

- Antihypertensive agents: enhanced antihypertensive effect and higher risk of postural hypotension (cumulative effects). For guanethidine, see below.
- Guanethidine: inhibition of the antihypertensive effect of guanethidine (guanethidine blocked from entering sympathetic nerve fiber, its site of action).
- Atropine and other atropine-like substances: imipramine antidepressants, anticholinergic H_1 antihistamines, anticholinergic antiparkinsonian agents, atropine like antispasmodics, disopyramide: cumulative adverse effects related to atropine-like substances as urinary retention, constipation, dry mouth, etc.
- Other central nervous system depressants: morphone derivates (analgesics, antitussives and replacement therapies); barbiturates; benzodiazepines; anxiolytics other than benzodiazepines (carbamates, captodiam, etifoxine); hypnotics; sedative antidepressants; sedative H_1 antihistamines; centrally active antihypertensive agents; baclofen; thalidomide: enhanced central nervous system depression. Impaired alertness may make driving vehicles and using machines dangerous.

4.6 Pregnancy and lactation

Phenothiazines should only be used during pregnancy if it is considered essential by the physician. Animal studies showed some detrimental effects on gestation in rats possibly secondary to hormonal interferences.

4.7 Effects on ability to drive and use machines

Phenothiazines may induce drowsiness. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

Starting at low doses:

Autonomic disturbances:
- Postural hypotension.
- Anticholinergic effects such as dry mouth, constipation and paralytic ileus (See Section 4.4 Special Warnings and Precautions for Use), accommodation disorders, risk of urinary retention.

Neuropsychiatric disorders:
- Sedation or drowsiness, more pronounced at the start of treatment.
- Indifference, anxiety reactions, mood changes.

At higher doses:

Neuropsychiatric disorders:
- Early-onset dyskinesia (spasmodic torticollis, oculogyric crises, trismus, etc)
- Tardive dyskinesia may occur in patients on long term therapy.

Anticholinergic antiparkinsonian agents have no effect or may cause exacerbation.

- Extrapyramidal syndrome:
- akinetic symptoms with or without hypertonia partially resolving with anticholinergic antiparkinsonian agents,
- hyperkinetic-hypertonic symptoms, excitatory motor behavioural activity,
- akathisia.

Endocrine and metabolic disorders:

- Hyperprolactinaemia: amenorrhoea, galactorrhoea, gynaecomastia, impotence, frigidity.
- Alteration in temperature regulation.
- Weight gain.
- Elevated blood glucose levels, alteration in glucose tolerance.

Dose dependent and rarely reported:

Cardiac disorders:
- QT interval prolongation, ventricular arrhythmias such as torsade de points, ventricular tachycardia which may result in ventricular fibrillation or cardiac arrest.
- There have been isolated reports of sudden death, with possible causes of cardiac origin (See Section 4.4), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Non-dose dependent and more rarely reported:

Skin disorders:
- Allergic skin reactions.
- Photosensitisation.

Haematological disorders:
- Very rare cases of agranulocytosis: regular complete blood counts are recommended.
- Leukopenia.

Ophthalmological disorders:
- Brownish deposits in the anterior segment of the eye due to accumulation of the product and generally without effect on vision.

Other disorders observed:
Positive titre for antinuclear antibodies without clinical lupus erythematosus.
Possible cholestatic jaundice.
Neuroleptic malignant syndrome (See section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Overdosage can cause severe parkinsonism syndrome and coma. Treatment should be symptomatic in a specialised unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A slow release phenothiazine neuroleptic.

5.2 Pharmacokinetic properties

Prolonged T½ of up to 16 days.

5.3 Preclinical safety data

There is no other information available which could be of relevance to the prescriber in recognising the safety profile of PIPORTIL and which is not included in the relevant sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sesame oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in original container in order to protect the product from light.

6.5 Nature and contents of container

1 ml clear Type 1 glass ampoule packed 10 per cardboard carton.

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

Single dose container, discard after use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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