Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depixol 40mg/2ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml ampoule contains 40mg (2% w/v) cis (z)-flupentixol decanoate (equivalent to 20mg/ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, yellowish, sterile oily solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The management of schizophrenia and allied paranoid psychoses.

4.2 Posology and method of administration

Route of administration: Deep intramuscular injection into the upper outer buttock or lateral thigh. Dosage and dosage interval should be adjusted according to the patients' symptoms and response to treatment.

Note: As with all oil based injections it is important to ensure, by aspiration before injection, that inadvertent intravascular entry does not occur.

Adults: The usual dose is between 20 to 40 mg every two to four weeks. Larger doses may be used if necessary, distributed between two injection sites.

In patients who have not previously received depot neuroleptics, treatment is usually started with a small dose (e.g. 20 mg) to assess tolerability. An interval of at least one-week should be allowed before the second injection is given at a dose consistent with the patients' condition.

Adequate control of severe psychotic symptoms may take up to 4 to 6 months at high enough dosage. Once stabilised lower maintenance doses may be considered, but must be sufficient to prevent relapse.

The appropriate presentation of Depixol should be selected to achieve an injection volume, which does not exceed 2 ml. Volumes greater than 2 ml should be distributed between two injection sites.

When transferring patients from oral to depot neuroleptic treatment, the oral medication should not be discontinued immediately, but gradually withdrawn over a period of several days after administering the first injection.

Elderly: Dosage should be at the lowest limit of the range.

Children: Depixol Injection is not indicated for children.

4.3 Contraindications

Use in patients who have proved intolerant of thioxanthenes.
Use in children.
Use in senile confusional states.
Use in patients who are excitable or over active.
Use in comatose states.

4.4 Special warnings and precautions for use

Caution should be exercised in patients having: liver disease; cardiac disease or arrhythmias; severe respiratory disease; renal failure; epilepsy (and conditions predisposing to epilepsy e.g. alcohol withdrawal or brain damage); Parkinson's disease; hypothyroidism; hyperthyroidism; myasthenia gravis; phaeochromocytoma.

The elderly require close supervision because they are especially prone to experience such adverse effects as sedation, hypotension, confusion and temperature changes.

The following warning applies to therapeutic class of antipsychotics. Avoid concomitant use of other antipsychotics. Flupentixol should be used with caution in patients with cardiovascular disease or family history of QT prolongation.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other neuroleptics, flupentixol enhances the response to alcohol, and the effects of barbiturates and other CNS depressants, and may potentiate the effects of general anaesthetics. Neuroleptics may antagonise the effects of adrenaline and other sympathomimetic agents, and reverse the antihypertensive effects of guanethidine and similar adrenergic-blocking agents. Neuroleptics may impair the effect of levodopa, adrenergic drugs and anticonvulsants. The metabolism of tricyclic antidepressants may be inhibited and the control of diabetes may be impaired. The effect of anticoagulants may be increased. Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal symptoms. Neuroleptics may enhance the cardiac depressant effects of quinidine; the absorption of corticosteroids and digoxin; the hypotensive effect of vasodilator antihypertensive agents such as hydralazine and prolong the action of neuromuscular blocking agents. The possibility of interaction with lithium salts should be borne in mind.

The following interactions apply to the therapeutic class of antipsychotics.

- Concomitant use of QT prolonging drugs.
- Concomitant use of drugs causing electrolyte imbalance.

4.6 Pregnancy and lactation

As the safety of this drug during pregnancy has not been established, use during pregnancy, especially the first and last trimesters, should be avoided, unless the expected benefit to the patient outweighs the potential risk to the foetus.

Flupentixol is excreted into the breast milk. If the use of Depixol is considered essential, nursing mothers should be advised to stop breast-feeding.

The newborn of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyperexcitability, and have a low APGAR score.

4.7 Effects on ability to drive and use machines

Alertness may be impaired, especially at the start of treatment, or following the consumption of alcohol; patients should be warned of this risk and advised not to drive or operate machinery until their susceptibility is known.

4.8 Undesirable effects

Drowsiness and sedation are unusual. Sedation, if it occurs, is more often seen with high dosage and at the start of treatment, particularly in the elderly. Other adverse effects include blurring of vision, tachycardia and hypotension.

Extrapyramidal reactions in the form of acute dystonias (including oculogyric crisis), parkinsonian rigidity, tremor, akinesia and akathisia have been reported and may occur even at lower dosage in susceptible patients. Such effects would usually be encountered early in treatment, but delayed reactions may also occur. Antiparkinson agents should not be prescribed routinely because of the possible risk of precipitating toxic-confusional states, impairing therapeutic efficacy or causing anticholinergic side-effects. They should only be given if required and their requirement reassessed at regular intervals.

Tardive dyskinesia can occur with neuroleptic treatment. It is more common at high doses for prolonged periods but has been reported at lower dosage for short periods. The risk seems to be greater in the elderly, especially females. It has been reported that fine vermicular movements of the tongue are an early sign. It has been observed occasionally in patients receiving Depixol. The concurrent use of anticholinergic antiparkinson drugs may exacerbate this effect. The potential irreversibility and seriousness, as well as the unpredictability of the syndrome, requires especially careful assessment of the risk versus benefit, and the lowest possible dosage and duration of treatment consistent with therapeutic efficacy. Short-lived dyskinesia may occur after abrupt withdrawal of the drug.

The neuroleptic malignant syndrome has rarely been reported in patients receiving neuroleptics, including flupentixol. This potentially fatal syndrome is characterised by hyperthermia, a fluctuating level of consciousness, muscular rigidity and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented.

Epileptic fits have occasionally been reported. Confusional states can occur.

The hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may be associated with galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea. Sexual function, including erection and ejaculation may be impaired; but increased libido has also been reported.

Flupentixol may impair body temperature control, and cases of hyperthermia have occurred rarely. The possible development of hypothermia, particularly in the elderly and hypothyroid, should be borne in mind.

Blood dyscrasias have occasionally been reported. Blood counts should be carried out if a patient develops signs of persistent infection. Jaundice and other liver abnormalities have been reported rarely.

Weight gain and less commonly weight loss have been reported; oedema has occasionally been reported and has been considered to be allergic in origin. Rashes have occurred rarely. Although less likely than with phenothiazines, flupentixol can rarely cause increased susceptibility to sunburn.

Occasional local reactions, such as erythema, swelling or tender fibrous nodules have been reported.

Flupentixol, even in low doses, in susceptible (especially non-psychotic) individuals may unusually cause nausea, dizziness or headache, excitement, agitation, insomnia, or unpleasant subjective feelings of being mentally dulled or slowed down.

If antipsychotic drugs are withdrawn, recurrence of psychotic symptoms may not become apparent for several weeks or months.

The following adverse reactions apply to the therapeutic class of antipsychotics.

- QT prolongation
- Ventricular arrhythmias- ventricular fibrillation (VF), ventricular tachycardia (VT) (rare)
- Sudden unexplained death
- Cardiac arrest
- Torsades de Pointes

4.9 Overdose

Overdosage may cause somnolence, or even coma, extrapyramidal symptoms, convulsions, hypotension, shock, hyper- or hypothermia. Treatment is symptomatic and supportive, with measures aimed at supporting the respiratory and cardiovascular systems.

The following specific measures may be employed if required:

- anticholinergic antiparkinson drugs if extrapyramidal symptoms occur.
- sedation (with benzodiazepines) in the unlikely event of agitation or excitement or convulsions.
- noradrenaline in saline intravenous drip if the patient is in shock. Adrenaline must not be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

cis(Z)-flupentixol is a neuroleptic of the thioxanthene series.
The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect. The thioxanthenes have high affinity for both the adenylate cyclase coupled dopamine D_1 receptors and for the dopamine D_2 receptors; in the phenothiazine group the affinity for D_1 receptors is much lower than that for D_2 receptors, whereas butyrophenones, diphenylbutylpiperidines and benzamides only have affinity for D_2 receptors.

In the traditional tests for antipsychotic effect, e.g. antagonism of stereotypic behaviour induced by dopamine agonists, the chemical groups of neuroleptics mentioned reveal equal but dosage-dependent activity. However, the antistereotypic effects of phenothiazines, butyrophenones, diphenylbutylpiperidines, and benzamides is strongly counteracted by the anticholinergic drug scopolamine, while the antistereotypic effect of thioxanthenes, e.g. cis(Z)-flupentixol is not, or only very slightly, influenced by concomitant treatment with anticholinergics.

5.2 Pharmacokinetic properties

By esterification of cis(Z)-flupentixol with decanoic acid cis(Z)-flupentixol has been converted to a highly lipophilic substance, cis(Z)-flupentixol decanoate. When dissolved in oil and injected intramuscularly this substance diffuses slowly into the surrounding body water, where enzymatic breakdown occurs releasing the active component cis(Z)-flupentixol. The duration of action is 2-4 weeks with maximum serum levels being reached by the end of the first week after injection.

cis(Z)-flupentixol is distributed in the body in a similar way to other neuroleptics; with the highest concentrations of drug and metabolites in liver, lungs, intestines and kidneys and lower concentrations in heart, spleen, brain and blood. The apparent volume of distribution is about 14 L/kg and the protein binding >95%.

cis(Z)-flupentixol crosses the placental barrier in small amounts; it is also excreted in breast milk in very small amounts.

The metabolism of cis(Z)-flupentixol proceeds via three main routes - sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. The excretion proceeds mainly with the faeces but also to some degree with the urine system; clearance is about 0.4-0.5 l/min.

5.3 Preclinical safety data

Nil of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain (Thin vegetable oil)

6.2 Incompatibilities

This product may be mixed in the same syringe with other products in the Depixol Injection range. It should not be mixed with any other injection fluids.

6.3 Shelf Life

4 years.
Once opened, use immediately. Discard any unused solution.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Clear glass (type I) ampoules of 2ml.
Pack size = 10 ampoules per box.

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

For single use only. Discard any remaining contents after use.

7 MARKETING AUTHORISATION HOLDER

Lundbeck Ltd.
Sunningdale House
Caldecotte Lake Business Park
Caldecotte
Milton Keynes MK7 8LF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 115/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 1976

Date of last renewal: 21 June 2006

10 DATE OF REVISION OF THE TEXT

June 2006