Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depixol 20mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 20 mg (2% w/v) cis(Z)-flupentixol decanoate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
Clear, colourless to slightly yellowish oil, practically free from particles.

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 dosage is between 20 to 40mg 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from oral to depot neuroleptic treatment, the oral medication should not be discontinued immediately but gradually withdrawn over a period of several days after administering the first injection.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 patients
Elderly patients should receive dosages in the lower end of the dosage range

Reduced renal function
Flupentixol decanoate can be given in usual doses to patients with reduced renal function.

Reduced hepatic function
Dose reduction (relative to the degree of hepatic impairment) should be considered. If possible, where assay facilities exist dosage should be adjusted according to serum levels.

Children
Flupentixol decanoate is not indicated for children

Method of administration

Flupentixol decanoate is administered by intramuscular injection into the upper outer quadrant of the gluteal region. Injection volumes exceeding 2 ml should be distributed between two injection sites.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
- Circulatory collapse
- Depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates)
- Coma
- Use in children
- Use in senile confusional states.

4.4 Special warnings and precautions for use

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 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 flupentixol. 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 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.

The possibility of development of neuroleptic malignant syndrome exists with any neuroleptic. The risk is possibly greater with the more potent agents. Patients with pre-existing organic brain syndrome, mental retardation and opiate and alcohol abuse are over-represented among fatal cases. Rare cases reported as NMS have also been received in association with flupentixol. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, sweating and cardiac arrhythmia). Additional signs may include elevated creatinine, phosphokinase, myoglubinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all neuropleptic medication, including flupentixol must be discontinued. Symptoms may persist for more than a week after oral neuroleptics are discontinued and somewhat longer when associated with the depot forms of the drugs.
Like other neuroleptics flupentixol decanoate should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic disease.

In the lower dosage range flupentixol decanoate is not recommended for excitable or overactive patients since its activating effect may lead to exaggeration of these characteristics.

Flupentixol should also be used with caution in patients with epilepsy (and conditions predisposing to epilepsy e.g. alcohol withdrawal or brain damage), severe respiratory disease and Parkinson's disease.

As described for other psychotropics flupentixol decanoate may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

The general caution for use of neuroleptics in hypothyroidism, thyrotoxicosis, myasthenia gravis or prostatic hypertrophy should be observed, but there is no evidence to suggest that flupentixol gives rise to any particular problem in such conditions.

Patients on long-term therapy, particularly on high doses, should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

As with other drugs belonging to the therapeutic class of antipsychotics, flupentixol decanoate may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, flupentixol decanoate should be used with caution in susceptible individuals (with hypokalemia, hypomagnesia or family history of QT prolongation) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (<50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with flupentixol decanoate and preventive measures undertaken.

Elderly
Care should also be taken in the elderly, particularly if frail or at risk of hypothermia, sedation, hypotension or confusion.

Cerebrovascular
An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Flupentixol decanoate should be used with caution in patients with risk factors for stroke.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Depixol is not licensed for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations requiring precautions for use
Flupentixol decanoate may enhance the sedative effect of alcohol, the effects of barbiturates and other CNS depressants, and may potentiate the effects of general anaesthetics.

Flupentixol decanoate may reduce the effect of levodopa, and the affect of adrenergic drugs.

Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal disorder.

Neuroleptics may increase or reduce the effect of antihypertensive drugs, the antihypertensive effect of guanethidine and similar acting compounds is reduced.

Concomitant use of neuroleptics and lithium increases the risk of neurotoxicity.

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other.

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.

As for other atypical antipsychotics, caution is advised in patients taking flupentixol in concomitant use with oral anticoagulants (e.g. warfarin), and other medicinal products known to affect platelet function (e.g. phenothiazines, most tricyclic antidepressants, acetylsalicyclic acid, and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole).

Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co−administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs should be avoided. Relevant classes include:

- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. terfenadine, astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase QT interval (e.g. cisapride, lithium) should be avoided.

Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalemia) and drugs known to increase the plasma concentration of flupentixol decanoate should also be used with caution as they may increase the risk of QT prolongation and malignant arrythmias (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with flupentixol.

Due to insufficient safety information in humans, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

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.

Animal reproduction studies on flupentixol have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproduction process.

Neonates exposed to antipsychotics (including flupentixol decanoate) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation
As flupentixol is found in breast milk in low concentrations, breast-feeding should not be continued during flupentixol decanoate therapy unless in the opinion of the physician the expected benefit to the patient outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

Flupentixol decanoate is a non-sedating drug in the low-moderate dosage range (up to 100 mg/2nd week). However,

patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

4.8 Undesirable effects

Undesirable effects are for the majority dose dependent. The frequency and severity are most pronounced in the early phase of treatment and decline during continued treatment.

Extrapyramidal reactions may occur, especially during the first few days after injection and in the early phase of treatment. In most cases these side effects can be satisfactorily controlled by reduction of dosage and/or use of antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesia and may aggravate them. Reduction in dosage or, if possible, discontinuation of flupentixol therapy is recommended. In persistent akathisia, a benzodiazepine or propranolol may be useful.

Frequencies are taken from the literature and spontaneous reporting. Frequencies are defined as:
very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

Cardiac disorders	Common	Tachycardia, palpitations.
	Rare	Electrocardiogram QT prolonged.
Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis
Nervous system disorders	Very common	Somnolence, akathisia, hyperkinesia, hypokinesia.
	Common	Tremor, dystonia, dizziness, headache.
	Uncommon to Rare	Tardive dyskinesia, dyskinesia, parkinsonism, speech disorder, convulsion.
	Very rare	Neuroleptic malignant syndrome.
Eye disorders	Common	Accommodation disorder, vision abnormal.
	Uncommon	Oculogyration.
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea.
Gastrointestinal disorders	Very common	Dry mouth.
	Common	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Uncommon	Abdominal pain, nausea, flatulence.
Renal and urinary disorders	Common	Micturition disorder, urinary retention.
Pregnancy, puerperium and perinatal conditions	Not Known	Drug withdrawal syndrome neonatal (see 4.6).

Skin and subcutaneous tissue disorders	Common	Hyperhidrosis, pruritus.
	Uncommon	Rash, photosensitivity reaction, dermatitis.
Musculoskeletal and connective tissue disorder	Common	Myalgia.
	Uncommon	Muscle rigidity.
Endocrine disorders	Rare	Hyperprolactinaemia.
Metabolism and nutrition disorders	Common	Increased appetite, weight increased.
	Uncommon	Decreased appetite.
	Rare	Hyperglycaemia, glucose tolerance abnormal.
Vascular disorders	Uncommon	Hypotension, hot flush.
	Very rare	Venous thromboembolism.
General disorders and administration site conditions	Common	Asthenia, fatigue.
	Uncommon	Injection site reaction.
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction.
Hepatobiliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Jaundice.
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea.
Psychiatric disorders	Common	Insomnia, depression, nervousness, agitation, libido decreased.
	Uncommon	Confusional state.

Localized erythema, pruritus and injection site nodule are the most typical injection site reactions.

As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for flupentixol decanoate (see section 4.4).

Abrupt discontinuation of flupentixol decanoate may be accompanied by withdrawal symptoms. The most common symptoms are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation. Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days.

4.9 Overdose

Due to the administration form, overdose symptoms are unlikely to occur.

Symptoms
Somnolence, coma movement disorders, convulsions, shock, hyperthermia or hypothermia.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when administered in overdose together with drugs known to affect the heart.

Treatment:
Treatment is symptomatic and supportive. Measures to support the respiratory and cardiovascular systems should be instituted. Adrenaline should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal symptoms with biperiden.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Neuroleptics (antipsychotics)
ATC code: N 05 AF 01

Mechanism of Action
Cis (Z)-flupentixol is a neuroleptic of the thioxanthene group.

The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect. It is also possible that 5-HT (5-hydroxytryptamine) receptor blockade contributes.

Cis (Z)-flupentixol has high affinity for both dopamine D_1 and D_2 receptors and for α_1-adrenoceptors and 5-HT_2 receptors.
Cis (Z)-flupentixol has no affinity for cholinergic muscarine receptors, only slight antihistaminergic properties and no α_2-adrenoceptor blocking activity.

Cis(Z)-flupentixol has proven to be a potent neuroleptic in all the behavioural studies for neuroleptic (dopamine receptor blocking) activity. Correlation is found in the *in vivo* test models, the affinity for dopamine D_2 binding sites *in vitro* and the average, daily oral antipsychotic doses.

Clinical efficacy
In clinical use flupentixol decanoate is intended for the maintenance treatment of chronic psychotic patients. The antipsychotic effect increases with increasing dosages. In low to moderate dosages (up to 100 mg/2 weeks) flupentixol decanoate is non-sedating while some unspecific sedation may be expected when higher doses are administered.

Flupentixol decanoate is particularly useful in the treatment of apathetic, withdrawn, depressed and poorly motivated patients.

Flupentixol decanoate permits continuous treatment especially of those patients who are unreliable in taking the oral medication prescribed for them. Flupentixol decanoate thus prevents the frequent relapses due to noncompliance in patients on oral medication.

5.2 Pharmacokinetic properties

Absorption
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 the ester diffuses rather slowly from the oil to the body water phase where it is rapidly hydrolysed releasing the active cis(Z)-flupentixol.

Following intramuscular injection maximum serum concentration is generally reached over a period of 3-7 days. With an estimated half-life of 3 weeks (reflecting the release from the depot) steady state conditions will be attained after

about 3 months' repeated administration.

Distribution
The apparent volume of distribution $(V_d)_\beta$ is about 14.1 l/kg. The plasma protein binding is about 99 %.

Biotransformation
The metabolism of cis(Z)-flupentixol proceeds along three main routes – sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. Cis(Z)-flupentixol dominates over metabolites in brain and other tissues.

Elimination
The elimination half-life ($T_{½\ \beta}$) of cis(Z)-flupentixol is about 35 hours and the mean systemic clearance (Cl_s) is about 0.29 l/min.
Cis(Z)-flupentixol is excreted mainly with faeces, but also to some degree with the urine. When tritium labelled flupentixol was administered to man the excretion pattern shows the excretion via faeces to be about 4 times the urinary excretion.

In nursing mothers cis(Z)-flupentixol is excreted in small amounts with the breast milk. The ratio milk conc./serum conc. in women is on an average 1.3.

Linearity
The kinetics is linear. The mean steady state pre-injection serum level of cis(Z)-flupentixol corresponding to a 40 mg dose of cis(Z)-flupentixol decanoate every two weeks is about 6 nmol/l.

Elderly patients
Pharmacokinetic investigations have not been done in elderly patients. However, for the related thioxanthene drug, zuclopenthixol, the pharmacokinetic parameters are widely independent of the age of the patients.

Reduced renal function
Based on the above characteristics for elimination it is reasonable to assume that reduced kidney function is likely not to have much influence on the serum levels of parent drug.

Reduced hepatic function
No data available.

Pharmacokinetic / Pharmacodynamic relationship
A pre-injection serum (plasma) concentration of 1-3 ng/ml (2-8 nmol/l) and a max./min. fluctuation < 2.5 is suggested as a guideline for maintenance treatment of schizophrenic patients with a low-moderate degree of illness.
Pharmacokinetically a dose of 40 mg/2 weeks of cis(Z)-flupentixol decanoate is equivalent to a daily oral dose of 10 mg flupentixol.

5.3 Preclinical safety data

Acute toxicity
Flupentixol has low acute toxicity.

Chronic toxicity
In chronic toxicity studies there were no findings of concern for the therapeutic use of flupentixol.

Reproduction toxicity
Flupentixol was tested for developmental toxicity in mice, rats, and rabbits by the oral route and cis-z-flupentixol decanoate was tested after subcutaneous (mice/rats) or intramuscular administration (rabbits). Under the conditions of these studies flupentixol and cis-z-flupentixol did not induce malformations or affect embryo-foetal viability.

Carcinogenicity
Flupentixol has no carcinogenic potential.

Local toxicity
The local tolerability is good. Local muscle damage is seen after injection of aqueous solutions of neuroleptics. After intramuscular injection in rabbits of cis(Z)-flupentixol decanoate in oil only slight haemorrhage and oedema was seen.

Cis(Z)-flupentixol has proven to be a potent neuroleptic in all the behavioural studies for neuroleptic (dopamine receptor blocking) activity. Correlation is found in the in vivo test models, the affinity for dopamine D2 binding sites in vitro and the average, daily oral antipsychotic dose.

Like most other neuroleptics, flupentixol increases the serum prolactin level.

Pharmacological studies have clearly demonstrated that cis(Z)-flupentixol decanoate in oil has a prolonged neuroleptic effect and that the amount of drug necessary to maintain a certain effect over a long period is considerably smaller with the depot preparation than with daily oral administration of flupentixol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products apart from other products in the Depixol range.

6.3 Shelf life

4 years.
Once opened, use immediately and discard any unused solution.

6.4 Special precautions for storage

Store below 25°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Colourless glass (type 1) ampoule of 1ml.
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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 115/1/1

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