פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

Summary of product characteristics - Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Fluanxol® Depot 20 mg /ml
Fluanxol® Depot 100 mg /ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flupentixol decanoate 20 mg/ml.
Flupentixol decanoate 100 mg/ml.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oily Solution for injection. Intramuscular (IM).

20 mg/ml: Clear, colourless to slightly yellowish oil, practically free from particles.
100 mg/ml: Clear, yellowish to yellow oil, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Schizophrenia and mania.

4.2 Posology and method of administration

Adults
Dosage and interval between injections should be adjusted for each individual patient so as to achieve a maximum suppression of psychotic symptoms with a minimum of side effects.

Flupentixol decanoate 20 mg/ml
In the maintenance treatment the dosage range would normally be 20-40 mg (1-2 ml) at intervals of 2 to 4 weeks depending on the response.
Some patients may need larger doses or need them at shorter intervals. Flupentixol decanoate 20 mg/ml is unsuitable for patients in whom sedation is required. Injection volumes larger than 2 ml should be distributed between two injection sites.

If volumes larger than 2-3 ml of the 20 mg/ml solution are required the more concentrated solutions (flupentixol decanoate 100 mg/ml) should be preferred.

During an exacerbation or acute relapse of the illness single injections of as much as 400 mg fortnightly (or in the occasional cases weekly for a short period) may be required.

Flupentixol decanoate 100 mg/ml
Dosage range lies between 50 mg (0.5 ml) every 4 weeks to 300 mg (3 ml) every 2 weeks but some patients may require up to 400 mg (4 ml) weekly. Injection volumes larger than 2 ml should be distributed between two injection sites.

Adequate control of severe psychotic symptoms by the concentrated injection fluids is usually achieved within 4 to 6 months and may justify gradual return to lower dose maintenance.

When changing the medication from oral flupentixol to maintenance treatment with flupentixol decanoate the following guidelines should be used:

x mg p.o. daily corresponds to 4x mg decanoate every 2 weeks.
x mg p.o. daily corresponds to 8x mg decanoate every 4 weeks.

Oral flupentixol should be continued during the first week after the first injection but in diminishing dosage.

Patients being transferred from other depot preparations should receive a dose in the ratio of 40 mg flupentixol decanoate equivalent to 25 mg fluphenazine decanoate, to 200 mg zuclopenthixol decanoate, or to 50 mg haloperidol decanoate.

Subsequent doses of flupentixol decanoate and interval between injections should be adjusted to the patient's response.

Older patients
Older 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 liver function
Careful dosing and, if possible, a serum level determination is advisable.

Children
Flupentixol decanoate is not recommended for use in children due to lack of clinical experience.

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. Local tolerability is good.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed section 6.1.
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Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma.

4.4 Special warnings and precautions for use
The possibility of development of neuroleptic malignant syndrome (hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system) 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.

Treatment: Discontinuation of the neuroleptic. Symptomatic treatment and use of general supportive measures.
Dantrolene and bromocriptine may be helpful.
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.

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

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 genetic predisposition) 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.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including .flupentixol decanoate
Long-acting depot antipsychotics should be used with caution in combination with other medicines known to have a myelosuppressive potential, as these cannot rapidly be removed from the body in .conditions where this may be required

Older people

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 Older people with Dementia
Data from two large observational studies showed that older 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.

Flupentixol decanoate 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 and the effects of barbiturates and other CNS depressants.

Neuroleptics may increase or reduce the antihypertensive 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.
Flupentixol decanoate may reduce the effect of levodopa and the effect of adrenergic drugs.
Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal symptoms.

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 thiazidediuretica (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
Flupentixol decanoate should not be administered during pregnancy unless the expected benefit to the patient outweighs the theoretical risk to the foetus.

Animal- studies have shown reproductive toxicity (see section 5.3-.

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.

Breast-feedingLactationAs flupentixol is found in breast milk in low concentrations it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is less than 0.5% of the weight related maternal dose (in mg/kg). Breast-feeding can be continued during flupentixol decanoate therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

Fertility
In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, libido decreased, erectile dysfunction and ejaculation failure have been reported (see section 4.8). These .events may have a negative impact on female and/or male sexual function and fertility

If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are .reversible on discontinuation

In preclinical fertility studies in rats, flupentixol slightly affected the pregnancy rate of female rats. Effects were seen at doses well in excess of those applied during clinical use
References: 319F , 275F , 23F
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4.7 Effects on ability to drive and use machines

Fluanxol Depot 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 (can not 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.

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/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.
Epinephrine (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)
ATCcode: N 05 AF 01

Mechanism of action
Flupentixol is a neuroleptic of the thioxanthene group.
The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect but possibly also 5-HT (5-hydroxytryptamine) receptor blockade contributes. *In vitro* and *in vivo* Flupentixol has high affinity for both dopamine D_1 and D_2 receptors whereas fluphenazine is almost D_2 selective *in vivo*. The atypical antipsychotic, clozapine, shows - as Flupentixol – equiaffinity to D_1 and D_2 receptors both *in vitro* and *in vivo*.

Flupentixol has high affinity for α_1-adrenoceptors and 5-HT_2 receptors, although lower than that of chlorprothixene, high-dose phenothiazines and clozapine, but no affinity for cholinergic muscarine receptors. It has only slight antihistaminergic properties and no α_2-adrenoceptor blocking activity.

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.

Perioral movements in rats are dependent on D_1 receptor stimulation or blockade of the D_2 receptor population. The movements can be prevented by Flupentixol. Likewise, the results form investigations in monkeys indicate that oral hyperkinesia is more related to D_1 receptor stimulation and to a less degree to D_2 receptor supersensitivity. This leads to the suggestion that D_1 activation is responsible for similar effects in man, i.e. dyskinesia. Therefore, blockade of D_1 receptors should be advantageous.

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

Pharmacological studies have clearly demonstrated that 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. A very modest and short-lasting potentiation of barbiturate-induced sleeping time in mice could be demonstrated only with high doses. It is unlikely, therefore, that any significant interference with anaesthetics would occur in patients receiving the depot preparation.

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 nonsedating 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 Flupentixol with decanoic acid Flupentixol has been converted to a highly lipophilic substance, 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 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 Flupentixol proceeds along three main routes – sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. Flupentixol dominates over metabolites in brain and other tissues.

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

In nursing mothers 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 Flupentixol corresponding to a 40 mg dose of Flupentixol decanoate every 2 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 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

In fertility studies in rats, flupentixol slightly affected the pregnancy rate of female rats. Effects .were seen at doses well in excess of those applied during clinical use
Animal reproduction studies in mice, rats and rabbits have not shown evidence of teratogenic effects. Embryotoxic effects in terms of increased post implantation loss/increased absorption rates .or occasional abortions were seen in rats and rabbits at doses associated with maternal toxicity
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 Flupentixol decanoate in oil only slight haemorrhage and oedema was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium-chain

6.2 Incompatibilities

Fluanxol Depot should not be mixed with depot formulations with sesame oil as the vehicle because this would result in definite changes in the pharmacokinetic properties of the involved preparations.

6.3 Shelf life and Special precautions for storage

Fluanxol Depot is valid for 4 years when stored at max 30°C. Keep ampoules in outer carton in order to protect from light.

Each pack has open expiry date.
Keep out of reach of children.

6.4 Nature and contents of container Glass ampoules in carton.

Fluanxol Depot 20 mg/ml:
Ampoules of 1 ml (20 mg)
Ampoules of 2 ml (40 mg)

Fluanxol Depot 100 mg/ml:
Ampoules of 1 ml (100 mg)

6.5 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MANUFACTURER

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8. LICENSE HOLDER
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9. DATE OF REVISION OF THE TEXT
JUNE 2014