PH-067-60-20-13411

Physician Information Leaflet

# Flupentixol Decanoate

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## 1. NAME OF THE MEDICINAL PRODUCT

**20 mg/mL Solution for Injection (I.M.)**

**Fluanxol® Depot**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20 mg Flupentixol decanoate, BP in Medium chain triglycerides.

## 3. PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless to slightly yellowish oil, practically free from particles.

## 4. CLINICAL PARTICULARS

Neuroleptic
A potent non-sedating neuroleptic for long-term therapy

**4.1 Therapeutic indications**
Schizophrenia and allied psychoses, especially with symptoms such as hallucinations, paranoid delusions and thought disturbances along with apathy, energy and withdrawal.

**4.2 Dosage regimen**
Adults:
Flupentixol decanoate is administered by intramuscular injection into the upper outer quadrant of the buttock. Local tolerability is good. Dosage and interval between injections should be individually adjusted according to the therapeutic response.

In the maintenance treatment, the dosage range would normally be 20-40 mg (1-2 mL) every 2-4 weeks. Some patients may need higher doses or shorter intervals between doses. Injection volumes exceeding 2 mL should be distributed between two injection sites. Those not previously treated with long-acting antipsychotic injections should continue with oral neuroleptic drugs but in diminishing dosage.

**4.3 Contraindications**
Hypersensitivity to the active substance or to any of the excipients in the formulation.

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**
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.

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

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.

An approximately 3-fold increased risk of cerebrovascular adverse events has 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 (CVA).

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.

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 Fluanxol Depot 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.

**4.5 Drug interactions**
Combinations requiring precautions for use
Flupentixol decanoate may enhance the sedative effect alcohol and the effects of barbiturates and other CNS depressants.

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.

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 disorder.

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 arrhythmias.

**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.

The newborns 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.

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.

Animal studies have shown reproductive toxicity.

*Lactation*
As 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.

**4.7 Effects on ability to drive or 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). Within each frequency group, undesirable effects are arranged following to decreased seriousness.

| System Organ Class | Frequency | Preferred term |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Thrombocytopenia, neutropenia, leukopenia, agranulocytosis |
| Immune system disorders | Rare | Hypersensitivity, anaphylactic reaction. |
| Endocrine disorders | Rare | Hyperprolactinaemia. |
| Metabolism and nutrition disorders | Common | Increased appetite, weight increased. |
| | Uncommon | Decreased appetite. |
| | Rare | Hyperglycaemia, glucose tolerance abnormal. |
| Psychiatric disorders | Common | Insomnia, depression, nervousness, agitation, libido decreased. |
| | Uncommon | Confusional state. |
| 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. |
| Cardiac disorders | Common | Tachycardia, palpitations. |
| | Rare | Electrocardiogram QT prolonged. |


Artwork & Master Data

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NEW MATERIAL
Material No.: 151509
Punch: 0640
Size/mm.: 190x400
PCR/CR No.: 932797

COLOUR SPECIFICATIONS
Black

Notice: Colour matching of this print is only to be used as a guideline.

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| Vascular disorders | Uncommon | Hypotension, hot flush. |
| | Very rare | Venous thromboembolism |
| 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. |
| Hepatobiliary disorders | Uncommon | Liver function test abnormal. |
| | Very rare | Jaundice. |
| Skin and subcutaneous tissue disorders | Common | Hyperhidrosis, pruritus. |
| | Uncommon | Rash, photosensitivity reaction, dermatitis. |
| Musculoskeletal and connective tissue disorder | Common | Myalgia. |
| | Uncommon | Muscle rigidity. |
| Renal and urinary disorders | Common | Miction disorder, urinary retention |
| Pregnancy, puerperium and perinatal conditions | Not known | Drug withdrawal syndrome neonatal (see 4.6) |
| Reproductive system and breast disorders | Uncommon | Ejaculation failure, erectile dysfunction. |
| | Rare | Gynaecomastia, galactorrhoea, amenorrhoea. |
| General disorders and administration site conditions | Common | Asthenia, fatigue. |
| | Uncommon | Injection site reaction. |

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.

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, hyper- 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. 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),
ATC code: N05AF01

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 but possibly also 5-HT (5-hydroxytryptamine) receptor blockade contributes. In vitro and in vivo cis(Z)-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 cis(Z)-flupentixol – equiaffinity to $D_1$ and $D_2$ receptors both in vitro and in vivo.

Cis(Z)-flupentixol has high affinity for $\alpha_1$-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 $\alpha_2$-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.

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 cis(Z)-flupentixol. Likewise, the results from 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 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. 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 Pharmacokinetics**
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 (Vd)β 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 ($T_{½}$ β) of cis(Z)-flupentixol is about 35 hours and the mean systemic clearance (Cls) is about 0.29 l/min.
Cis(Z)-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 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 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 cis(Z)-flupentixol decanoate is equivalent to a daily oral dose of 10 mg flupentixol.

**5.3 Pre-clinical 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 cis(Z)-flupentixol decanoate in oil only slight haemorrhage and oedema was seen.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 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**
4 years

**6.4 Storage conditions**
Store at temperatures not exceeding 30˚C, protected from light.

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

**6.5 Nature and contents of container**
*Availability*
1 mL Clear Glass Ampoule (Box of 10's)

**6.6 Special precautions for disposal**
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**6.7 Caution**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
For suspected adverse drug reaction, report to the FDA:www.fda.gov.ph.
Patient is advised to seek medical attention immediately at the first sign of any adverse drug reaction that shall appear.

## 7. MARKETING AUTHORISATION HOLDER

**Manufactured by:**
H. Lundbeck A/S
Ottiliavej 9,
Valby, 2500, Denmark

**Imported and distributed by:**
METRO DRUG,INC.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna, Philippines

## 8. MARKETING AUTHORISATION NUMBER(S)

DR-XY3945

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

International birth date: 26 March 1970

Date of first authorisation in PH: 8 August 1986

Date of last renewal: 1 July 2021

## 10. DATE OF REVISION OF THE TEXT

16th February 2021