Fluanxol Depot
flupentixol decanoate)

A potent non-sedating neuroleptic for long-term therapy

1. NAME OF THE MEDICINAL PRODUCT

Fluanxol Depot 20mg/ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

flupentixol decanoate 20mg/ml

3. PHARMACEUTICAL FORM

Solution for injection (injection).
20mg/ml: Clear, colourless to slightly yellowish oil, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Maintenance treatment of schizophrenia and other psychoses, especially with symptoms such as hallucinations, delusions and thought disturbances along with apathy, lack of energy, and withdrawal.

4.2 Posology and method of administration

Posology
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 20mg/ml
In the maintenance treatment the dosage range would normally be 20-40mg (1-2ml) 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 20mg/ml is unsuitable for patients in whom sedation is required. Injection volumes larger than 2ml should be distributed between two injection sites.

If volumes larger than 2-3ml of the 20mg/ml solution are required the more concentrated solution (flupentixol decanotae 100mg/ml or 200mg/ml) should be preferred.

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

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 Fluanxol 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 40mg flupentixol decanoate equivalent to 25mg fluphenazine decanoate, to 200mg zuclopenthixol decanoate, or to 50mg haloperidol decanoate.

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

Elderly patients
The pharmacokinetics, safety and efficacy of flupentixol in elderly patients with schizophrenia have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population.

Reduced renal function
Based on the 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 liver function
Flupentixol has not been studied in hepatic impairment. It is extensively metabolized by the liver and particular caution should be used in this situation and serum level monitoring is advised. Fluanxol should be initiated at low doses orally to check for tolerability before switching to the depot formulation.

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 2ml should be distributed between two injection sites. Local tolerability is good.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the exicipients (listed in section 6.1).

Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturate or opiate); 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 possibility 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.

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 hyokalemia, 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.

Elderly

Cerebrovascular
An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized 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 in 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 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 if 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- feeding
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). Breastfeeding 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 and use machines

Fluanxol Depot is a non-sedating drug. 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 symptoms may occur, especially in the early phase of treatment. In most cases these side effects can be satisfactorily controlled by reduction of dosage and/ or antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesias 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 defiend 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).

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.
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	Micturition 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 (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, extrapyramidal symptoms, convulsions, hypotension, shock, hyperthermia/ hypothermia.

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 D1 and D2 receptors whereas fluphenazine is almost D2 selective in vivo. The atypical antipsychotic, clozapine,
shows - as Flupentixol – equiaffinity to D1 and D2 receptors both in vitro and in vivo.

Flupentixol has high affinity for α1-adrenoceptors and 5-HT2 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 α2-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 D2 binding sites in vitro and the average, daily oral antipsychotic doses.

Perioral movements in rats are dependent on D1 receptor stimulation or blockade of the D2 receptor population. The movements can be prevented by Flupentixol. Likewise, the results form investigations in monkeys indicate that oral hyperkinesia is more related to D1 receptor stimulation and to a less degree to D2 receptor supersensitivity. This leads to the suggestion that D1 activation is responsible for similar effects in man, i.e. dyskinesia. Therefore, blockade of D1 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.

Detailed Pharmacology
Flupentixol reduces spontaneous activity in mice and induces a cataleptic state as determined by the vertical rod test. The drug antagonizes amphetamine-induced stereotyped behaviour and apomorphine-induced compulsive gnawing in rats as well as methylphenidate-induced compulsive gnawing in mice. It is also effective in preventing apomorphine-induced emesis in dogs.
Flupentixol inhibits the conditioned and, at higher doses, the unconditioned avoidance response in rats. It is also effective in releasing conflict-suppressed behaviour in rats. Flupentixol provides some protection against amphetamine-induced stimulation prolongs alcohol- and barbiturate-induced sleeping time in mice in only very high doses indicating a very weak sedative action in clinical use. It protects rats against isoniazid and pentetrazol convulsions, and, in higher doses, against electroconvulsions. Flupentixol displays very weak anticholinergic activity in isolated

guinea pig ileum and weak adrenolytic activity. It does not inhibit monoamine oxidase, nor does it inhibit the reuptake of adrenergic transmitters of adrenergic nerve endings. Flupentixol antagonizes the effect of dopamine on cyclic AMP in the olfactory tubule and nucleus accumbens in the rat and antagonizes the dopamine agonist 2-amino-6,7-dihydroxyl-1,2,3,4,tetrahydro-napthalene in the striatum. With the exception of minor drops in blood pressure seen when the drug is given by the intravenous route, it is without effect on the cardiovascular system of dogs. Blood pressure was also reduced by flupentixol in anesthetized rats and cats. Like most other neuroleptics, flupentixol inhibits the prolactin inhibiting factor, resulting in an increase in serum prolactin levels.

Clinical efficacy and safety

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:
The esterification of flupentixol results in the slow release of the drug from the injection site with consequent prolongation of duration of action. Studies in rats and dogs with 3H-flupentixol decanoate have revealed that flupentixol decanoate diffuses slowly from the oil solution into the extracellular fluid from where it is distributed via the blood stream to the different tissues of the body. In pharmacokinetic studies measuring flupentixol blood levels, peak concentrations of the drug were found between days 4 and 7, following intramuscular injections of 40 mg of Fluanxol Depot 2% or 10%. It could still be detected in the blood three weeks after injection.

Distribution:
The highest levels of flupentixol as reflected by radioactivity count are found in the lungs, liver, and spleen, while concentrations in the brain are considerably lower, and only a little higher than concentrations found in the blood.
The apparent volume of distribution (Vd)β is about 14.1 l/kg. The plasma protein binding is about 99%.

Metabolism:
Flupentixol is metabolized by sulfoxidation, dealkylation (splitting of the distal ethanolic group in the side chain) and conjugation to glucuronic acid. The metabolites of flupentixol are devoid of psychopharmacological activity.

Flupentixol decanoate is efficiently hydrolized in vivo to flupentixol which is present in all tissues of the body.

Excretion:
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. The half-life of the drug calculated from excretion data has been shown to be eight days for the rat and about 12 days for the dog. Peak serum levels occur within the first 24 hours in rats and at 7 days after injection in dogs, but significant levels of radioactivity are found up to five weeks after administration.
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 flupentixol decanoate is equivalent to a daily oral dose of 10 mg flupentixol.

5.3 Preclinical safety data

Acute toxicity
The parenteral LD50 of flupentixol decanoate is greater than 200 mg/kg in rats. Mice administered 400 mg/kg orally or parenterally survived for three days. The majority died between the fourth and tenth day after becoming sedated and being unable to eat or drink.

Subacute and Chronic toxicity
10 or 15 mg/kg of flupentixol decanoate was administered twice weekly to rats for seven weeks. It was associated with some inhibition of growth secondary to sedation causing reduced food

intake, a decrease in red blood cells (males only), and an increase in serum creatinine. At post mortem, the only significant finding, apart from a slight decrease in liver weight in males, was a localized subcutaneous reaction around the oil droplets. During a ten-week recovery period the oil droplets disappeared gradually, but not completely.

Dogs were administered 0, 2 and 6 mg/kg/week intramuscularly for 26 weeks. The only significant findings were a heavy local reaction with some encapsulated small oil drops at the injection site, slight swelling of the popliteal gland (16th week), some inter- and intramuscular fibrosis with hyperplasia of the popliteal lymph node and an apparently dose-related transient increase in alpha globulins with concurrent decrease in beta and gamma globulins.

Reproductive 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.

Flupentixol decanoate was administered on day 6 of gestation to mice and rats (10 and 20 mg/kg s.c.) and to rabbits (2 and 6 mg/kg i.m.). Dams were not adversely affected. However, an abortificacient effect occurred in mice receiving 20 mg/kg.
In reproductive studies with flupentixol hydrochloride, a similar abortifacient effect was noted in mice and rabbits. In rats, fetotoxic effects (reduced conception rates, increased resorptions, retarded growth and poor weaning performances) were observed. Four cases of cleft palate were found in three litters of rats receiving 50 or 25 mg/kg/day.

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
Vegetable oil

6.2 Incompatibilities

Flupentixol decanoate 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 Special precautions for storage

Store below 30oC.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

20 mg/ml
Colourless glass (type I) ampoules of 1 ml and 2 ml.
Boxes of 1×1 ml, 10×1 ml, 1×2 ml and 10×2 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHOTISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

Date of revision of text: May 2014