1. NAME OF THE MEDICINAL PRODUCT

Fluanxol 0.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluanxol 0.5 mg: Each tablet contains 0.5 mg flupentixol (as 0.5840 mg flupentixol dihydrochloride

Excipients with known effect:

Lactose monohydrate

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

0.5mg: Round, slightly biconvex, yellow, film-coated tablet marked FD.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression involving anxiety, asthenia and lack of initiative.

Chronic neuroses with anxiety, depression, and inactivity.

Psychosomatic disorders with asthenic reactions.

Acute and situational anxiety and tension states in which a sedative/hypnotic effect is not required and especially when the patient is considered in danger of abusing minor tranquillizers

4.2 Posology and method of administration

Posology

Adults

Initially 1 mg daily as a single morning dose or 0.5 mg twice daily. After one week the dosage may be increased to 2 mg daily if there is inadequate clinical response. Daily dosage of more than 2 mg should be in divided doses up to a maximum of 3 mg.

Patients often respond to flupentixol within two or three days. If no effect has been observed within one week of maximum dosage (3 mg daily) the drug should be withdrawn.

Older patients

Older patients should receive half the recommended dosages. The initial dosage for older patient is 0.5 mg as a single morning dose. After one week, if response is inadequate, dosage may be increased to 1 mg daily. Caution should be exercised in further increasing the dosage but occasional patients may require up to a maximum of 1.5 mg a day which should be given in divided doses.

Reduced renal function

Flupentixol has not been studied in renal impairment. Increased cerebral sensitivity to antipsychotics has been noted in severe renal impairment.

Reduced liver function

Flupentixol has not been studied in hepatic impairment. It is extensively metabolised by the liver and particular caution should be used in this situation and serum level monitoring is advised.

Children

Not recommended for children

Method of administration

The tablets are swallowed with water.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in, see section 6.1.
Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma.
Not recommended for excitable or agitated patients

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 drug.

Like other neuroleptics flupentixol should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic disease.

Not recommended for excitable or overactive patients in doses up to 25 mg/day since its activating effect may lead to exaggeration of these characteristics. If previously the patient has been treated with tranquillizers or neuroleptics with sedative effect, these should be withdrawn gradually.

As described for other psychotropics flupentixol 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 may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, flupentixol 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).

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which flupentixol is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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 and preventive measures undertaken

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

Excipients

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.
3 mg and 5 mg tablets also contain Sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interactions with other medicinal products and other forms of interactions

In common with other similar drugs, flupentixol enhances the response to alcohol, the effects of barbiturates and other CNS depressants. Flupentixol may potentiate the effects of general anaesthetics and anticoagulants and prolong the action of neuromuscular blocking agents.

The anticholinergic effects of atropine or other drugs with anticholinergic properties may be increased. Concomitant use of drugs such as metoclopramide, piperazine or antiparkinson drugs may increase the risk of extrapyramidal effects such as tardive dyskinesia. Combined use of antipsychotics and lithium or sibutramine has been associated with an increased risk of neurotoxicity.

Antipsychotics 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 α-blockers (e.g. doxazosin), or methyl-dopa may be enhanced.

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 should also be used with caution as they may increase the risk of QT prolongation and malignant arrythmias (see section 4.4).

Antipsychotics may antagonise the effects of adrenaline and other sympathomimetic agents, and reverse the antihypertensive effects of guanethidine, possibly clonidine and similar adrenergic-blocking agents. Antipsychotics may also impair the effect of levodopa, adrenergic drugs and anticonvulsants.

The metabolism of tricyclic antidepressants may be inhibited and the control of diabetes may be impaired.

4.6 Fertility, pregnancy and lactation

Pregnancy

Neonates exposed to antipsychotics during the third trimester of pregnancy are at risk of extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited. In other cases neonates have required intensive care unit support and prolonged hospitalization. .

Fluanxol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Animal studies have shown reproductive toxicity (see section 5.3)

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 daily dose. Breast-feeding can be continued during flupentixol 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 is a non-sedating drug in the low-moderate dosage range.
Alertness may be impaired, especially at the start of treatment, or following the consumption of alcohol; patients should be warned of this risk and advised not to drive or operate machinery until their susceptibility is known. Patients should not drive if they have blurred vision.

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 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).

Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutroppenia, 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.
	Not known	Suicidal ideation, suicidal behaviour *)
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 thromboemlisme
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.

*) Cases of suicidal ideation and suicidal behaviours have been reported during flupentixol therapy or early after treatment discontinuation (see section 4.4).

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 (see section 4.4).

Abrupt discontinuation of flupentixol 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

Symptoms:

Somnolence, coma, movement disorder, convulsions, shock, hyperthermia/hypothermia.

The highest orally administered single dose in clinical trials was 80 mg, and up to 320 mg/day has been given.

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. Gastric lavage should be carried out as soon as possible after oral ingestion and activated charcoal may be administered. 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: N 05 AF 01

Mechanism of action

Flupentixol is a neuroleptic of the thioxanthene group.

Flupentixol is a mixture of two geometric isomers, the active flupentixol and trans(E)-flupentixol, approximately in the ratio of 1:1.

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 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.

Flupentixol prolongs alcohol- and barbiturate-induced sleeping time in mice in only very high doses indicating a very weak sedative action in clinical use.

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

Clinical efficacy and safety

In clinical use flupentixol has a broad spectrum of activity that varies according to the dosage.

Flupentixol in low dosages (1-2 mg/day) has antidepressant, anxiolytic and activating effects.

In moderate dosages (3-25 mg/day) flupentixol is intended for the treatment of acute and chronic psychoses. In this dosage range flupentixol has practically no unspecific sedative effect and is not suited for patients with severe psychomotor agitation. Besides causing a significant reduction or complete elimination of the nuclear symptoms of schizophrenia such as hallucinations, delusions and thought disturbances flupentixol also has disinhibiting (antiautistic and activating) and mood-elevating properties making flupentixol particularly useful in the treatment of apathetic, withdrawn, depressed and poorly motivated patients.
The antipsychotic effect increases with increasing dosage; in addition some sedation should be anticipated. Flupentixol has within the whole dosage range a pronounced anxiolytic effect and even in high-dose treatment the mood elevating and disinhibiting effects of flupentixol are retained. High dose treatment does not increase the frequency of extrapyramidal symptoms.

5.2 Pharmacokinetic properties

The following data concerns the active cis(Z)-isomer.

Absorption
Oral administration results in maximum serum levels in about 4-5 hours. Oral bioavailability is about 40 %.

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 ($T_{½\,\beta}$) is about 35 hours and the mean systemic clearance (Cl_s) is about 0.29 l/min.
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 showed the excretion via faeces 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. Steady state plasma levels are achieved in about 7 days. The mean minimum steady state level corresponding to 5 mg flupentixol orally once-a-day was about 1.7 ng/ml (3.9 nmol/l).

Older patients
Pharmacokinetic investigations have not been done in older 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 minimum (i.e. concentration measured just before administration of a dose) serum (plasma) concentration of 1-3 ng/ml (2-8 nmol/l) is suggested as a guideline for maintenance treatment of schizophrenic patients with a low-moderate degree of illness.

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.

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.

Carcinogenicity
Flupentixol has no carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Betadex,
Lactose monohydrate,
Maize starch,
Hydroxypropyl cellulose,
Microcrystalline cellulose,
Croscarmellose sodium,
Talc,
Vegetable oil, hydrogenated,

Magnesium stearate

Coating and colour:
Polyvinyl alcohol, partly hydrolyzed,
Titanium dioxide (E171),
Macrogol/PEG 3350,
Talc,
Iron oxide yellow (E172),
Macrogol/PEG6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

0.5 mg: 100 in blisters

6.6 Special precautions for disposal

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

7. MANUFACTURER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark.

8. Product Registration Holder

Lundbeck Malaysia Sdn. Bhd.
A-05-01, Oasis Square,
Jalan PJU 1A/7A, Ara Damansara,
47301 Petaling Jaya, Selangor Darul Ehsan.

9. DATE OF REVISION OF THE TEXT

August 2022