

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluanxol 1 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg flupentixol present as flupentixol dihydrochloride.

Excipients: Also includes lactose monohydrate 19.85 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Oval, slightly biconvex, yellow, film-coated tablet marked FF.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term management of mild to moderate depression with or without anxiety.

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 an inadequate clinical response. Daily dosage of more than 2 mg should be divided doses up to a maximum of 3 mg.

Older people

Older people should receive half the recommended dosages, i.e. 0.5 – 1.5 mg daily.

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 If no effect has been observed within one week of maximum dosage the drug should be withdrawn.

Children:

Fluanxol is not recommended for use in children due to lack of clinical experience.

Reduced renal function

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

Reduced hepatic function

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

Method of administration

The tablets are swallowed with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates)
- Coma
- Senile confusional states
- Severe depression
- Patients who have proved intolerant of thioxanthenes or related drugs.

4.4 Special warnings and precautions for use

Administration to patients with Parkinsonism or extrapyramidal disorder may induce an exacerbation of that disorder. Extrapyramidal reactions in the form of acute dystonias (including oculogyric crisis), parkinsonian rigidity, tremor, akinesia and akathisia have been reported and may occur even at lower dosage in susceptible patients. Such effects would usually be encountered early in treatment, but delayed reactions may also occur. Antiparkinson agents should not be prescribed routinely because of the possible risk of precipitating toxic-confusional states, impairing efficacy or causing anticholinergic side-effects. They should only be given if required and their requirement reassessed at regular intervals.

Tardive dyskinesia can occur with neuroleptic treatment. It is more common at high doses for prolonged periods but has been reported at lower dosage for short periods. The risk seems to be greater in older people, especially females. It has been reported that fine vermicular movements of the tongue are an early sign. It has been observed occasionally in patients receiving flupentixol. The concurrent use of anticholinergic antiparkinson drugs may exacerbate this effect. The potential irreversibility and seriousness, as well as the unpredictability of the syndrome, requires especially careful assessment of the risk versus benefit, and the lowest possible dosage and duration of treatment consistent with therapeutic efficacy. Short-lived dyskinesia may occur after abrupt withdrawal of the drug.

The hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may be associated with galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea. Sexual function, including erection and ejaculation may be impaired; but increased libido has also been reported.

The possibility of development of neuroleptic malignant syndrome (NMS) (hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system) exists with any neuroleptic. Patients with pre-existing organic brain syndrome, mental retardation, opiate or alcohol abuse are over-represented among fatal cases. Rare cases reported as NMS have also been received in association with flupentixol. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, sweating and cardiac arrhythmia). Additional signs may include elevated creatinine, phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all neuroleptic medication, including flupentixol must be discontinued.

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.

Flupentixol should be used with great caution in patients with severe atherosclerosis, myocardial insufficiency or severe hepatic or renal insufficiency.

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

As with other drugs that belong 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, hypomagnesaemia 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).

Suicide/suicidal thoughts or clinical worsening

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.

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.

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

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

Recurrence of depression symptoms on abrupt withdrawal is rare. However, gradual reduction of dosage is advisable. Dependence has not been reported to date.

As described for other neuroleptics flupentixol may modify insulin and glucose responses calling for adjustment of antidiabetic therapy in patients with diabetes.

Flupentixol may initially cause drowsiness. Patients should be warned of this possibility if driving or operating machinery. Alcohol may potentiate this effect (see section 4.7).

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

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

Care should also be taken in older people, particularly if frail or at risk of hypothermia, sedation, hypotension or confusion.

Cerebrovascular

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

Fluanxol 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.

4.5 Interaction with other medicinal products and other forms of interactionCombinations requiring precautions for use

Flupentixol may initially cause drowsiness and may enhance the sedative effect of alcohol, barbiturates, other central nervous system depressants, and general anaesthetics. Patients should be warned of this possibility if driving or operating machinery (see section 4.7).

Flupentixol may reduce the effect of levodopa and the effect of adrenergic drugs.

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

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

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

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

Neuroleptics may enhance the cardiac depressant effects of quinidine; the absorption of corticosteroids and digoxin; the hypotensive effect of vasodilator antihypertensive agents such as hydralazine and prolong the action of neuromuscular blocking agents.

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

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

Relevant classes include:

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

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

Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalaemia) 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 arrhythmias (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Animal studies have shown reproductive toxicity (see section 5.3)

Neonates exposed to antipsychotics (including flupentixol) 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, breast-feeding should not be continued during flupentixol therapy unless in the opinion of the physician the expected benefit to the patient outweighs the potential risk to the infant.

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 clinically 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

Flupentixol may initially cause drowsiness. Patients should be warned of this possibility if driving or operating machinery. Alcohol may potentiate this effect (see section 4.4).

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 (cannot 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.
	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 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.

¹Cases of suicidal ideation and suicidal behaviours have been reported during Fluanxol 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 arrhythmias - 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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. 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

Flupentixol is a mixture of two geometric isomers, the active *cis*(Z)-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.

Cis(Z)-flupentixol has high affinity for α_1 -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 α_2 -adrenoceptor blocking activity.

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

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)_p 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 ($T_{1/2\beta}$) 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 people

Pharmacokinetic investigations have not been done in older people. 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 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC blisters of 60 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Lundbeck Ltd.
Building K1 Timbold Drive
Kents Hill
Milton Keynes MK7 6BZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0115/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st December 1982

Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

June 2015