PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

FLUANXOL® DEPOT

Injection 20 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FLUANXOL DEPOT Injection contains cis (Z)-flupenthixol decanoate 20 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLUANXOL DEPOT is indicated in the maintenance management of schizophrenic patients especially those who are unreliable in taking the medication prescribed for them.

4.2 Posology and method of administration

Posology

Adults

FLUANXOL DEPOT is administered by deep intramuscular injection in the gluteal region, usually in doses of 20 - 60 mg (1 - 3 ml) at intervals of 2 - 4 weeks, depending on response.

Certain patients may need larger doses, or need them at shorter intervals.

4.3 Contraindications

- Hypersensitivity to flupenthixol decanoate or any other component of the formulation.

- Extremely excitable and overactive patients.
- Circulatory collapse, depressed level of consciousness due to any cause (e.g. barbiturate, alcohol and opiate poisoning), coma.
- Pregnancy and lactation (see Section 4.6)
- Phaeochromocytoma
- Bone marrow suppression

4.4 Special warnings and precautions for use

Neuroleptic malignant syndrome may occur. The symptoms are: hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system.

Treatment:

- Discontinuation of FLUANXOL DEPOT.
- Symptomatic treatment and use of general supportive measures.
- Dantrolene and bromocriptine may be helpful.

Symptoms may persist for longer than a week after discontinuation of FLUANXOL DEPOT.

Increased mortality has been observed more often in patients with pre-existing organic brain syndrome, mental retardation, and opiate and alcohol abuse.

Patients on long-term therapy should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

FLUANXOL DEPOT may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of life threatening cardiac dysrhythmias, resulting in an increased risk of death. Therefore, FLUANXOL DEPOT should be used with caution in susceptible individuals (with hypokalaemia, 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 dysrhythmia. Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

Cases of venous thromboembolism (VTE) have been reported. All possible risk factors for VTE should be identified before and during treatment with FLUANXOL DEPOT and preventive measures undertaken.

Elderly

Cerebrovascular - An approximately 3-fold increased risk of cerebrovascular accident (stroke) has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is unknown. An increased risk cannot be excluded for other antipsychotics or other patient populations.

FLUANXOL DEPOT 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 an 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 should not be used for the treatment of dementia-related behavioural disturbances.

Caution should be exercised in patients having: liver disease; cardiac disease or dysrhythmias; severe respiratory, disease; renal failure; epilepsy (and conditions predisposing to epilepsy e.g. alcohol withdrawal or brain damage); Parkinson's disease; narrow angle glaucoma; prostatic hypertrophy; hypothyroidism; hyperthyroidism; myasthenia gravis; and patients who have shown hypersensitivity to thioxanthenes or other antipsychotics.

FLUANXOL DEPOT should be used with caution in patients with organic brain syndrome, convulsions and advanced hepatic disease.

FLUANXOL DEPOT may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

Regular eye examinations are advisable for patients receiving long-term FLUANXOL DEPOT therapy and avoidance of undue exposure to sunlight is recommended.

Haematological parameters should be monitored periodically.

4.5 Interaction with other medicines and other forms of interaction

Combinations requiring precaution for use

- FLUANXOL DEPOT may enhance the sedative effect alcohol and the effects of barbiturates and other CNS depressants.

- FLUANXOL DEPOT may increase or reduce the effect of antihypertensive agents.
- Concomitant use of FLUANXOL DEPOT and lithium increases the risk of neurotoxicity.
- Tricyclic antidepressants and FLUANXOL DEPOT mutually inhibit the metabolism of one another.
- FLUANXOL DEPOT may reduce the effect of levodopa and the effect of adrenergic agents.
- Concomitant use of FLUANXOL DEPOT with 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 agents known to significantly increase the QT interval and should be avoided.

Relevant classes include:

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

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

Medicines known to cause electrolyte disturbances such as thiazide diuretica (hypokalaemia) and medicines known to increase the plasma concentration of flupenthixol should also be used with caution as they may increase the risk of QT prolongation and cardiac dysrhythmias, resulting in an increased risk of death (see Section 4.4).

4.6 Fertility, pregnancy and lactation

FLUANXOL DEPOT should not be administered during pregnancy or lactation.

Pregnancy

The newborns of mothers treated with FLUANXOL DEPOT 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 FLUANXOL DEPOT) 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.

Breastfeeding

Flupenthixol is excreted into the breast milk. Mothers on treatment with FLUANXOL DEPOT should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

Patients for whom FLUANXOL DEPOT is prescribed should be cautioned about their ability to drive or operate machinery.

4.8 Undesirable effects

Extrapyramidal reactions may occur.

Tardive dyskinesia may develop.

In the listing below the definition of a Frequent event is either very common or common event (>1/100); all other events defined as Less frequent.

Organ class	**Frequency**	**Preferred term**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Less frequent	Hyperprolactinaemia
Metabolism and nutrition disorders	Frequent	Increased appetite, weight increased
	Less frequent	Decreased appetite, hyperglycaemia, abnormal glucose tolerance
Psychiatric disorders	Frequent	Insomnia, depression, nervousness, agitation, decreased libido
	Less frequent	Confusional state
Nervous system disorders	Frequent	Somnolence, akathisia, hyperkinesia, hypokinesia, tremor, dystonia, dizziness, headache
	Less frequent	Tardive dyskinesia, dyskinesia, parkinsonism, speech disorder, convulsions, neuroleptic malignant syndrome
Eye disorders	Frequent	Accommodation disorder, abnormal vision
	Less frequent	Oculogyration
Cardiac disorders	Frequent	Tachycardia, palpitations
	Less frequent	Electrocardiogram QT prolonged
Vascular disorders	Less frequent	Hypotension, hot flushes, venous thromboembolism

Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Dry mouth, salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea
	Less frequent	Abdominal pain, nausea, flatulence
Hepatobiliary disorders	Less frequent	Abnormal Liver function test, jaundice
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, pruritus
	Less Frequent	Rash, photosensitivity reaction, dermatitis
Musculoskeletal and connective tissue disorder	Frequent	Myalgia
	Less frequent	Muscle rigidity
Renal and urinary disorders	Frequent	Micturition disorder, urinary retention
Pregnancy, puerperium and perinatal conditions	Less frequent	Neonatal withdrawal syndrome (see section 4.6)
Reproductive system and breast disorders	Less frequent	Ejaculation failure, erectile dysfunction, gynaecomastia, galactorrhoea, amenorrhoea
General disorders and administration site conditions	Frequent	Asthenia, fatigue
	Less frequent	Injection site reaction

Cases of QT prolongation, ventricular dysrythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for FLUANXOL DEPOT (see Section 4.4).

Abrupt discontinuation of FLUANXOL DEPOT 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms:

Somnolence, coma, movement disorders, convulsions, shock, hyperthermia/hypothermia.
ECG changes, QT prolongation, Torsades de Pointes, cardiac arrest and ventricular dysrrhythmias have been reported when FLUANXOL DEPOT is administered in overdose or when administered together with medicines 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 2.6.5 Miscellaneous Structures (Thioxanthenes)

Flupenthixol is a neuroleptic of the thioxanthene group.

PROFESSIONAL INFORMATION

Flupenthixol has an anxiolytic, antidepressive mood-stabilising effect and certain activating properties. Flupenthixol is mainly effective through a blockade of central monoamine receptors, especially in the dopaminergic system.

5.2 Pharmacokinetic properties

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.

The maximal serum concentration is seen by the end of the first week after injection of FLUANXOL DEPOT in contrast to a peak 3 - 6 hours after FLUANXOL by mouth. Pharmacokinetically a weekly dose of 25 mg FLUANXOL DEPOT is equivalent to a daily oral dose of 10 mg FLUANXOL.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium-chain

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

48 months

6.4 Special precautions for storage

Store at or below 30 ºC.

Protect from light.

Keep out of reach of children.

Keep ampoules in outer carton in order to protect from light.

6.5 Nature and contents of container

Ampoules for injection:

1 x 1 ml

5 x 1 ml

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

G/2.6.5/138

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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