SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

PENTIXOL 40(FLUPENTIXOL INJECTION BP 40MG/2ML)

2. Qualitative and quantitative composition

Each 2ml contains:

Flupentixol Decanoate BP 40mg

3. Pharmaceutical form

Solution for injection

Clear, slightly yellowish oily liquid.

4. Clinical particulars

4.1 Therapeutic indications

The treatment of schizophrenia and other psychoses.

4.2 Posology and method of administration

Posology

Adults

The usual dosage of flupentixoldecanoate lies between 50 mg every 4 weeks and 300 mg every 2 weeks, but some patients may require up to 400 mg weekly. The maximum single dose at any one time is 400 mg. For example, 800 mg ever 2 weeks should not be given. Other patients may be adequately maintained on dosages of 20-40 mg flupentixoldecanoate every 2-4 weeks. In patients who have not previously received depot antipsychotic, treatment is usually started with a small dose (e.g. 20 mg) to assess tolerability. An interval of at least one week should be allowed before the second injection is given at a dose consistent with the patients' condition.

Flupentixol Injection 20 mg/ml is not intended for use in patients requiring doses of greater than 60 mg (3 ml) of flupentixol. Injection volumes of 2 – 3 ml should be distributed between two injection sites.

More concentrated solutions of flupentixoldecanoate (Flupentixol Conc Injection or Flupentixol Low Volume Injection) should be used if doses greater than 3 ml (60 mg) are required.

The injection volumes selected for Flupentixol Conc Injection or Flupentixol Low Volume Injection should not exceed 2 ml.

Adequate control of severe psychotic symptoms may take up to 4 to 6 months at high enough dosage. Once stabilised lower maintenance doses may be considered, but must be sufficient to prevent relapse.

Older patients

In accordance with standard medical practice, initial dosage may need to be reduced to a quarter or half the normal starting dose in the frail or older

patients.

Children

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

Patients with reduced renal function

Flupentixol has not been studied in renal impairment. Increased cerebral sensitivity to antipsychotics has been noted in severe renal impairment (see section 4.4).

Patients with reduced hepatic 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 (see section 4.4). Flupentixol should be initiated at low doses orally to check for tolerability before switching to the depot formulation.

Method of administration

Route of administration: For Deep intramuscular injection only

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. 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

Caution should be exercised in patients having: liver disease; cardiac disease or arrhythmias; 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; phaeochromocytoma and patients who have shown hypersensitivity to thioxanthenes or other antipsychotics.

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 overrepresented 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.

Blood dyscrasias, including thrombocytopenia, have been reported rarely. Blood counts should be carried out if a patient develops signs of persistent infection.

As described for other psychotropicsflupentixol may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. The plasma concentrations of the Flupentixol Injection and Conc. Injection gradually decrease over several weeks which makes gradual dosage tapering unnecessary.

When transferring patients from oral to depot antipsychotic treatment, the oral medication should not be discontinued immediately, but gradually withdrawn over a period of several days after administering the first injection.

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 hypokalaemia, 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.

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.

Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including flupentixoldecanoate.

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.

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. 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.

Older people

The elderly require close supervision because they are specially prone to experience such adverse effects as sedation, hypotension, confusion and temperature changes.

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.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antipsychotics, 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
- some quinolone antibiotics (e.g. 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 arrythmias.

Antipsychotics may antagonise the effects of adrenaline and other sympathomimetic agents, and reverse the antihypertensive effects of guanethidine 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.

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4.6 Fertility, pregnancy and lactation

Pregnancy

As the safety of this drug during pregnancy has not been established, use during pregnancy, especially the first and last trimesters, should be avoided, unless the expected benefit to the patient outweighs the potential risk to the foetus.

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.

Animal studies have shown reproductive toxicity (see section 5.3). Breast-feeding

Flupentixol is excreted into the breast milk. If the use of Flupentixol is considered essential, nursing mothers should be advised to stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

Increased appetite, weight increased.
Insomnia, depression, nervousness, agitation, libido decreased. Somnolence, akathisia, hyperkinesia, hypokinesia.
Tremor, dystonia, dizziness, headache, disturbance in attention. Accommodation disorder, vision abnormal.
Tachycardia,

palpitations.
Dyspnoea.
Dry mouth.
Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
Hyperhidrosis, pruritus.
Myalgia.
Micturition disorder, urinary retention.
Asthenia, fatigue.

Reporting of adverse Effects

Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdosage may cause somnolence or even coma, extrapyramidal symptoms, convulsions, hypotension, 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 is symptomatic and supportive, with measures aimed at supporting the respiratory and cardiovascular systems. The following specific measures may be employed if required.

- Anticholinergic antiparkinson drugs if extrapyramidal symptoms occur

- Sedation (with benzodiazepines) in the unlikely event of agitation or excitement or convulsions

- Noradrenaline in saline intravenous drip if the patient is in shock. Adrenaline must not be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Neuroleptics (antipsychotics), ATC code: N05AF01 Mechanism of action

Flupentixol is a non-sedating antipsychotic drug of the thioxanthene group. Its primary pharmacological action is dopamine blockade. Flupentixol has a high affinity for D1 and D2 receptors. Flupentixol Injection contains the deconoic ester of flupentixol in thin vegetable oil.

5.2 Pharmacokinetic properties
After intramuscular injection, the ester is slowly released from the oil depot and is rapidly hydrolysed to release flupentixol. Flupentixol is widely distributed in the body and extensively metabolized in the liver. Peak circulating levels occur around 7 days after administration.

5.3 Preclinical safety data
Reproductive toxicity

In fertility studies in rats, flupentixol slightly affected the pregnancy rate of female rats. 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.

6. Pharmaceutical particulars

6.1 List of excipients
As per dossier

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Store below 25°C. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml ampoule placed in tray such one tray packed in carton with an insert.

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

7. Marketing authorization holder

Krishna Chemists Limited,
Industrial area, Lusaka Road,3 rd floor, Metrix Hardware,
P.O Box 3328-00506, Nairobi
Kenya

Manufactured at:
Armein Pharmaceuticals Private Ltd.
Survey # 494, Dharmaj - Khambhat Road, At Bamanva Ta. Khambhat, Gujarat388580
India.

8. Marketing authorization number

H2024/CTD10794/23864

9. Date of first registration/ renewal of the registration

26/02/2024

10. Date of Revision Of The Text

26/02/2024