Professional Information / Package Insert

CLOPIXOL DEPOT Injection

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

CLOPIXOL DEPOT Injection

COMPOSITION:

CLOPIXOL DEPOT Injection is a 200 mg/ml sterile solution of zuclopenthixol decanoate intended for intramuscular injection.

The other ingredient is triglycerides, medium chain.

CATEGORY AND CLASS:

A 2.6.5 Miscellaneous Structures (Thioxanthenes)

PHARMACOLOGICAL ACTION:

CLOPIXOL DEPOT acts as a combined absorption and conversion depot. Absorption depots retain the active substance, releasing it gradually. In conversion depots the active substance is made available as a derivative which is slowly converted to the active substance. By the esterification of zuclopenthixol with decanoic acid, zuclopenthixol has been converted into a highly lipophilic substance, zuclopenthixol decanoate. When dissolved in oil and injected intramuscularly this substance diffuses slowly into the surrounding aqueous tissue fluids, where it undergoes enzymatic breakdown into the active component zuclopenthixol and decanoic acid.

Zuclopenthixol is a neuroleptic of the thioxanthene group.

It is relatively short-acting whereas CLOPIXOL DEPOT - the decanoic acid ester of zuclopenthixol - has a considerably prolonged action.

According to pharmacological and pharmacokinetic animal experiments the effect of CLOPIXOL DEPOT lasts for 10 days to 3 weeks after intramuscular injection, except for the cataleptogenic action which is rather weak and of appreciably shorter duration. Significant serum levels of zuclopenthixol are maintained throughout the dosage interval.

INDICATIONS:

Maintenance treatment of schizophrenia including agitation, psychomotor disturbances, hostility, suspiciousness, aggression and affective reactions.

CONTRA-INDICATIONS:

Hypersensitivity to the active substance or to any of the excipients, listed under composition.

Acute alcohol, barbiturate and opiate poisoning.

CLOPIXOL DEPOT should not be administered to pregnant patients (see Human reproduction: Pregnancy).

Patients suffering from or with a history of hepatic disease.

WARNINGS AND SPECIAL PRECAUTIONS:

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

CLOPIXOL DEPOT should be used with caution in patients with, convulsive disorders or advanced hepatic, renal or cardiovascular disease.

Neuroleptic malignant syndrome may occur. Symptoms may be: hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system.

Treatment:

- Discontinuation of CLOPIXOL DEPOT.
- 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 agents.

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

CLOPIXOL DEPOT may cause QT prolongation.
Persistently prolonged QT intervals may increase the risk of cardiac dysrhythmias, resulting in an increased risk of death. Therefore, CLOPIXOL DEPOT 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 dysrhythmia. Concomitant treatment with other antipsychotics should be avoided (see Interactions).

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

Leukopenia, neutropenia and agranulocytosis have been reported with CLOPIXOL DEPOT. 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.

Older people

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 not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. CLOPIXOL DEPOT 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 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.

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

CLOPIXOL DEPOT is not recommended for use in children due to a lack of clinical experience.

Effects on ability to drive and use machines

Alcohol tolerance and the ability to drive motor vehicles and operate machines may be affected. Therefore, caution should be exerted initially, until the individual reaction to the treatment is known.

INTERACTIONS:

Combinations requiring precautions for use

CLOPIXOL DEPOT may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

CLOPIXOL DEPOT should not be given concomitantly with guanethidine or similar acting compounds, since neuroleptics may block the antihypertensive effect of these compounds.

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

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of one another.
CLOPIXOL DEPOT may reduce the effect of levodopa and the effect of adrenergic agents.
Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal symptoms.

Since zuclopenthixol is partly metabolised by CYP2D6 concomitant use of drugs known to inhibit this enzyme may lead to decreased clearance of zuclopenthixol.

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. Co-administration of such agents 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 thiazidediuretics (hypokalemia) and medicines known to increase the plasma concentration of zuclopenthixol decanoate 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 Warnings and special precautions).

HUMAN REPRODUCTION:

Pregnancy

CLOPIXOL DEPOT should not be administered to pregnant patients.

Neonates exposed to CLOPIXOL 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.

Breast-feeding

Zuclopenthixol is excreted into breast milk. Mothers on CLOPIXOL DEPOT therapy should not breast-feed their babies.

Fertility

In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported (see Side effects). 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.

Administration of CLOPIXOL to male and female rats were associated with a slight delay in mating. In an experiment where CLOPIXOL was administered via the diet, impaired mating performance and reduced conception rate was noted.

DOSAGE AND DIRECTIONS FOR USE:

CLOPIXOL DEPOT is administered by deep intramuscular injection into the gluteal region, as a rule in doses of 200 - 400 mg (1 - 2 ml) at 2 - 4 week intervals. A few patients need higher doses or shorter intervals.

Treatment is usually started with 100 mg (½ ml) intramuscularly.
One week later, or when the symptoms recur (but not more than 4 weeks later) the second injection of 100 - 200 mg (½ - 1 ml) intramuscularly or more is administered.

During maintenance therapy 100 - 600 mg (½ - 3 ml) is given intramuscularly every 1 - 4 weeks, usually 200 mg (1 ml) every 2 - 4 weeks.

SIDE EFFECTS:

Extrapyramidal reactions may occur.

Tardive dyskinesias, may occur.

In the listing below a Frequent event is defined as either a very common

or common event (>1/100); all other events are 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, weight decreased, hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.
Psychiatric disorders	Frequent	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Less frequent	Apathy, nightmare, libido increased, confusional state.
Nervous system disorders	Frequent	Somnolence, akathisia, hyperkinesia, hypokinesia, tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.
	Less frequent	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine, neuroleptic malignant syndrome.
Eye disorders	Frequent	Accommodation disorder, abnormal vision. .
	Less frequent	Oculogyration, mydriasis.
Ear and labyrinth disorders	Frequent	Vertigo.
	Less frequent	Hyperacusis, tinnitus.
Cardiac disorders	Frequent	Tachycardia, palpitations.
	Less frequent	Electrocardiogram QT prolonged.

Vascular disorders	Less frequent	Hypotension, hot flush, venous thromboembolism.
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Frequent	Dry mouth, salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Less frequent	Abdominal pain, nausea, flatulence.
Hepato-biliary disorders	Less frequent	Liver function test abnormal, cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, pruritus.
	Less frequent	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Frequent	Myalgia.
	Less frequent	Muscle rigidity, trismus, torticollis.
Renal and urinary disorders	Frequent	Micturition disorder, urinary retention, polyuria.
Pregnancy, puerperium and perinatal conditions.	Less frequent	Drug withdrawal syndrome neonatal (see Pregnancy).
Reproductive system and breast disorders	Less frequent	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness, gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions	Frequent	Asthenia, fatigue, malaise, pain.
	Less frequent	Thirst, injection site reaction, hypothermia, pyrexia.

Cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for CLOPIXOL DEPOT (see Warnings and special precautions).

Abrupt discontinuation of CLOPIXOL 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Zuclopenthixol decanoate is a thioxanthene analogue of perphenazine.

Symptoms:

Overdosage may lead to chlorpromazine-like extrapyramidal symptoms, somnolence, coma, movement disorders, convulsions, shock and hyperthermia/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

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.

IDENTIFICATION:

Clear, yellowish, oil, practically free form particles.

PRESENTATION:

Colourless glass ampoules of 200 mg/ml: 1 x 1 ml, 5 x 1 ml

STORAGE INSTRUCTIONS:

Store at or below 30 ºC.

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

Keep out of reach of children.

REGISTRATION NUMBER:

R/2.6.5/52

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF

REGISTRATION:

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