

Clopi[®]xol Depot 200 mg/ml
(zuclopenthixol decanoate)

1. NAME OF THE MEDICINAL PRODUCT

Clopi[®]xol Depot 200 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zuclopenthixol decanoate 200 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

200 mg/ml: Clear, yellowish oil, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maintenance treatment of schizophrenia and other psychoses, especially with symptoms such as hallucinations, delusions and thought disturbances along with agitation, restlessness, hostility and aggressiveness.

4.2 Posology and method of administration

Posology

Adults

Dosage and interval between injections should be individually adjusted according to the condition of the patient. This in order to achieve a maximum suppression of psychotic symptoms with a minimum of side effects.

Zuclopenthixol decanoate 200 mg/ml

In the maintenance treatment the dosage range would normally be 200-400 mg (1-2 ml) every second to fourth week.

A few patients may need higher doses or shorter intervals between doses. Injection volumes exceeding 2 ml should be distributed between 2 injection sites.

If volumes larger than 2-3 ml of the 200 mg/ml solution are required, the more concentrated solution (zuclopenthixol decanoate 500 mg/ml) should be preferred.

When changing the medication from oral zuclopenthixol or zuclopenthixol acetate i.m. to maintenance treatment with zuclopenthixol decanoate the following guidelines should be used:

1) Change from oral zuclopenthixol to zuclopenthixol decanoate

x mg p.o. daily corresponds to 8x mg decanoate every 2 weeks.

x mg p.o. daily corresponds to 16x mg decanoate every 4 weeks.

Oral zuclopenthixol should be continued during the first week after the first injection but in diminishing dosage.

2) Change from zuclopenthixol acetate to zuclopenthixol decanoate

Concomitantly with the (last) injection of zuclopenthixol acetate (100 mg), 200-400 mg (1-2 ml) of zuclopenthixol decanoate 200 mg/ml should be given intramuscularly and repeated every 2nd week. Higher doses or shorter intervals may be needed.

Zuclopenthixol acetate and zuclopenthixol decanoate can be mixed in a syringe and given as one injection (co-injection).

Patients being transferred from other depot preparations should receive a dose in the ratio of 200 mg zuclopenthixol decanoate equivalent to 25 mg fluphenazine decanoate, to 40 mg cis(Z)-flupentixol decanoate, or to 50 mg haloperidol decanoate.

Subsequent doses of zuclopenthixol decanoate and interval between injections should be adjusted to the response of the patient.

Older patients

Older patients should receive dosages in the lower end of the dosage range.

Children

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

Reduced renal function

Clopixol Depot can be given in usual doses to patients with reduced renal function.

Zuclopenthixol is eliminated renally to a small extent (about 10 %, primarily as metabolites) which is why dose adjustment in patients with renal disease most likely is not necessary. However, there is limited experience with patients suffering from reduced renal function.

Reduced liver function

Careful dosing and, if possible, a serum level determination is advisable.

Method of administration

Clopixol Depot is administered by intramuscular injection into the upper outer quadrant of the gluteal region. Injection volumes exceeding 2 ml should be distributed between 2 injection sites. Local tolerability is good.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients, listed in (section 6.1).

Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma.

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

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

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 zuclopenthixol decanoate and preventive measures undertaken

Leukopenia, neutropenia and granulocytosis have been reported with antipsychotics, including zuclopenthixol decanoate.

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 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. Zuclopenthixol decanoate 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combinations requiring precautions for use

Zuclopenthixol decanoate may enhance the sedative effect of alcohol and the effects of barbiturates and other CNS depressants.

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.

Zuclopenthixol decanoate may reduce the effect of levodopa and the effect of adrenergic drugs.

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

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 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 (hypokalemia) and drugs 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 malignant arrhythmias (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Zuclopenthixol decanoate should not be administered during pregnancy unless the expected benefit to the patient outweighs the theoretical risk to the foetus.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for 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 hospitalisation.

Clopixol Depot 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 zuclopenthixol 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 1% of the weight related maternal dose (in mg/kg). Breast-feeding can be continued during zuclopenthixol decanoate 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, 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.

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

4.7 Effects on ability to drive and use machines

Clopixol Depot is a sedative drug. Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

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 during the first few days after an injection and 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 zuclopenthixol 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$), or not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
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Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction.
Endocrine disorders	Rare	Hyperprolactinaemia.
Metabolism and nutrition disorders	Common	Increased appetite, weight increased.
	Uncommon	Decreased appetite, weight decreased.
	Rare	Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state.
Nervous system disorders	Very common	Somnolence, akathisia, hyperkinesia, hypokinesia.
	Common	Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.
	Uncommon	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine.
	Very rare	Neuroleptic malignant syndrome.
Eye disorders	Common	Accommodation disorder, vision abnormal.
	Uncommon	Oculogyration, mydriasis.
Ear and labyrinth disorders	Common	Vertigo.
	Uncommon	Hyperacusis, tinnitus.
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	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Very common	Dry mouth.
	Common	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Uncommon	Abdominal pain, nausea, flatulence.
Hepato-biliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis, pruritus.
	Uncommon	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Common	Myalgia.
	Uncommon	Muscle rigidity, trismus, torticollis.
Renal and urinary disorders	Common	Micturition disorder, urinary retention, polyuria.
<u>Pregnancy, puerperium and perinatal conditions.</u>	<u>Not known</u>	<u>Drug withdrawal syndrome neonatal (see 4.6)</u>
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions	Common	Asthenia, fatigue, malaise, pain.
	Uncommon	Thirst, injection site reaction, hypothermia, pyrexia.

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 zuclopenthixol decanoate (see section 4.4).

Abrupt discontinuation of zuclopenthixol decanoate 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

Due to the administration form overdose symptoms are unlikely to occur.

Symptoms

Somnolence, coma, movement disorders, convulsions, shock, 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. Convulsions may be treated with diazepam and movement disorders with biperiden.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Neuroleptics (antipsychotics)

ATC-code: N 05 AF 05

Mechanism of action

Zuclopenthixol is a neuroleptic of the thioxanthene group.

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* zuclopenthixol has high affinity for both dopamine D1 and D2 receptors, for 1-adrenoceptors and 5-HT₂ receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H₁) receptor affinity and no 2-adrenoceptor blocking activity.

In vivo the affinity for D₂ binding sites dominates over the affinity for D₁ receptors. Zuclopenthixol 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 zuclopenthixol increases the serum prolactin level.

Pharmacological studies have clearly demonstrated that zuclopenthixol decanoate in oil has a prolonged neuroleptic effect and that the amount of drug necessary to maintain a certain effect over a long period is considerably smaller with the depot preparation than with daily oral administration of zuclopenthixol. In terms of clinical use, the findings in pharmacological studies may indicate that a prolonged neuroleptic effect without overt sedation may be obtained with the depot preparation. Moreover, the risk of interference with anaesthetics may be expected to be low.

Clinical efficacy and safety

In clinical use zuclopenthixol decanoate is intended for the maintenance treatment of chronic psychotic patients.

Positive results also have been obtained in the management of hyperactive and aggressive mentally handicapped patients.

Zuclopenthixol decanoate induces a transient dose-dependent sedation. However, if the patient is switched to maintenance treatment with zuclopenthixol decanoate from oral zuclopenthixol or from i.m. zuclopenthixol acetate the sedation will be no problem. Tolerance to the unspecific sedative effect develops rapidly.

Zuclopenthixol decanoate is particularly useful in the treatment of patients, who are agitated, restless, hostile, or aggressive.

Zuclopenthixol decanoate permits continuous treatment especially of those patients who are unreliable in taking the oral medication prescribed for them. Zuclopenthixol decanoate thus prevents the frequent relapses due to noncompliance in patients on oral medication.

5.2 Pharmacokinetic properties

Absorption

By esterification of zuclopenthixol with decanoic acid zuclopenthixol has been converted to a highly lipophilic substance, zuclopenthixol decanoate. When dissolved in oil and injected intramuscularly the ester diffuses rather slowly from the oil to the body water phase where it is rapidly hydrolysed releasing the active zuclopenthixol.

Following intramuscular injection maximum serum concentration is 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.

Distribution

The apparent volume of distribution (V_d) is about 20 l/kg. The plasma protein binding is about 98-99 %.

Biotransformation

The metabolism of zuclopenthixol proceeds along three main routes -sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. Zuclopenthixol dominates over metabolites in brain and other tissues.

Elimination

The elimination half-life ($T_{1/2}$) of zuclopenthixol is about 20 hours and the mean systemic clearance (Cl_s) is about 0.86 l/min.

Zuclopenthixol is excreted mainly with faeces, but also to some degree (about 10 %) with the urine. Only about 0.1 % of the dose is excreted unchanged with the urine, meaning that the drug load on the kidneys is negligible. In nursing mothers zuclopenthixol is excreted in small amounts with the breast milk. In steady state the pre-dose mean ratio milk conc./serum conc. in women treated orally or with the decanoate was about 0.29.

Linearity

The kinetics is linear. The mean steady state pre-injection serum level of zuclopenthixol corresponding to a 200 mg dose of zuclopenthixol decanoate every 2 weeks is about 10 ng/ml (25 nmol/l).

Older patients

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.

Polymorphism An *in vivo* investigation has shown that some part of the metabolic pathways is subject to genetic polymorphism of the sparteine/debrisoquine oxidation (CYP2D6).

Pharmacokinetic / Pharmacodynamic relationship

A pre-injection serum (plasma) concentration of 2.8-12 ng/ml (7-30 nmol/l) and a max./min. fluctuation < 2.5 is suggested as a guideline for maintenance treatment of schizophrenic patients with a low-moderate degree of illness. Pharmacokinetically a dose of 200 mg/2 weeks or 400 mg/4 weeks of zuclopenthixol decanoate is equivalent to a daily oral dose of 25 mg zuclopenthixol.

5.3 Preclinical safety data

Acute toxicity

Zuclopenthixol has low acute toxicity.

Chronic toxicity

In chronic toxicity studies there were no findings of concern for the therapeutic use of zuclopenthixol.

Reproduction toxicity

In a three-generation study in rats a delay in mating was noted. Once mated there was no effect on fertility. In an experimental where zuclopenthixol was administered via the diet, impaired mating performance and reduced conception rate was noted.

Animal reproduction studies have not shown evidence of embryotoxic or teratogenic effects. In a peri/postnatal study in rats, dosages of 5 and 15 mg/kg/day resulted in an increase of stillbirths, reduced pup survival and delayed development of pups.

The clinical significance of these findings is unclear and it is possible that the effect on pups was due to neglect from the dams that were exposed to doses of zuclopenthixol producing maternal toxicity.

Mutagenicity and carcinogenicity

Zuclopenthixol has no mutagenic or carcinogenic potential. In a rat oncogenecity study 30 mg/kg/day for two years (top dosage) resulted in slight non-statistical increases in the incidence of mammary adenocarcinomas, pancreatic islet cell adenomas, carcinomas in females and thyroid parafollicular carcinomas. The slight increase in the incidence of these tumours is a common finding for D2 antagonists, which increase prolactin secretion when administered to rats. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear, but it is accepted as not predicting an oncogenic risk in patients.

Local toxicity

Local muscle damage is seen after injection of aqueous solutions of neuroleptics, including zuclopenthixol. The muscle damage shows a much higher degree after the aqueous solution of neuroleptics than after the oily solutions of zuclopenthixol acetate and zuclopenthixol decanoate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium-chain.

6.2 Incompatibilities

Zuclopenthixol decanoate should only be mixed with zuclopenthixol acetate, which also is dissolved in Triglycerides, medium-chain (Ph. Eur.).

Zuclopenthixol 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

200 mg/ml: 3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the ampoules in the outer box in order to protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

200 mg/ml

Colourless ampoules (Type I glass) of 1 ml. Boxes of 1×1 ml, 10×1 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

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Valby Denmark

Product Registration Holder

Lundbeck Malaysia Sdn. Bhd.

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8. DATE OF REVISION OF THE TEXT