SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clopixol Depot 200
Clopixol Depot 500

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopixol Depot 200:

Zuclopenthixol decanoate 200 mg/ml.

Clopixol Depot 500

Zuclopenthixol decanoate 500 mg/ml.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release solution for injection, IM.
200 mg/ml: Clear, yellowish oil, practically free from particles.
500 mg/ml: Clear, yellow oily fluid, practically free from particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Clopixol Depot Injection is a depot neuroleptic preparation designed for the maintenance treatment of acute and chronic schizophrenia and other paranoid psychoses, especially where compliance with oral medication is a problem.

4.2 Posology and method of administration

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 2ml (400 mg) should be distributed between two 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.

Treatment is usually started with 100 mg. One week later, or when symptoms recur (but not more than 4 weeks later) a second injection of 100-200 mg or more is given.

Zuclopenthixol decanoate 500 mg/ml

250-500 mg (½ ml - 1 ml) every one to four weeks, depending on the response.

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.

Elderly:

Elderly 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.

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.

Note:

As with all oily injections it is important to ensure by aspiration before injection, that inadvertent intravascular entry does not occur.

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

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.
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 Clopixol Depot 200 and Clopixol Depot 500 gradually decrease over several weeks which make 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.
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 should be used with caution in patients with organic brain syndrome, convulsions or advanced hepatic disease.
Blood dyscrasias have been reported rarely. Blood counts should be carried out if a patient develops signs of persistent infection.
As with other drugs belonging to the therapeutic class of antipsychotics, zuclopenthixol may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, zuclopenthixol 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.
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 Clopixol and preventive measures undertaken.
Concomitant treatment with other antipsychotics should be avoided (see section 4.5).
As described for other psychotropics zuclopenthixol may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.
Leukopenia, neutropenia and agranulocytosis 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

Older people require close supervision because they are especially prone to experience such adverse effects as sedation, hypotension, confusion and temperature changes.

Cerebrovascular

An approximately 3-fold increased risk of cerebrovascular adverse events 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.
Zuclopenthixol 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.
Clopixol Depot 200 and Clopixol Depot 500 are 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, zuclopenthixol enhances the response to alcohol, the effects of barbiturates and other CNS depressants.

Zuclopenthixol 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.

Concomitant use of zuclopenthixol and drugs known to cause QT prolongation or cardiac arrhythmias, such as tricyclic antidepressants or other antipsychotics should be avoided.

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 (hypokalemia) and drugs known to increase the plasma concentration of zuclopenthixol should also be used with caution as they may increase the risk of QT prolongation and malignant arrhythmias (see section 4.4).

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.

Since zuclopenthixol is partly metabolised by CYP2D6 concomitant use of drugs known to inhibit this enzyme may lead to higher than expected plasma concentrations of zuclopenthixol, increasing the risk of adverse effects and cardiotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Neonates exposed to antipsychotics (including Clopixol) 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 reproduction 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 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 was associated with a slight delay in mating. In an experiment where zuclopenthixol was administered via the diet, impaired mating performance and reduced conception rate were noted.

4.7 Effects on ability to drive and use machines

Zuclopenthixol is a sedative drug.

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

The majority of undesirable effects are 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 dyskinsea 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), or not known (can not 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, 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 medistianal 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.
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal (see 4.6)
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 (see section 4.4).

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

Abrupt discontinuation of zuclopenthixol 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdose

Symptoms: somnolence, coma, extrapyramidal symptoms, convulsions, hypotension, shock, hyper or hypothermia. ECG changes have been reported when administered in overdose together with drugs known to affect the heart.

Treatment: treatment is symptomatic and supportive. Measures aimed at supporting the respiratory and cardiovascular systems should be instituted. Adrenaline (epinephrine) must not be used in these patients. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Neuropleptics (antipsychotics), ATC Code: N05AF05

Mechanism of action

The action of zuclopenthixol, as with other antipsychotics is mediated through dopamine receptor blockade. Zuclopenthixol has a high affinity for D_1 and D_2 receptors and activity has been demonstrated in standard animal models used to assess antipsychotic action. Serotonergic blocking properties, a high affinity for alpha-adrenoreceptors and slight antihistamine properties have been observed.

5.2. Pharmacokinetic properties

After deep intramuscular injection of Clopixol, serum levels of zuclopenthixol increase during the first week and decline slowly thereafter. A linear relationship has been observed between Clopixol dosage and serum level. Metabolism proceeds by sulphoxidation, dealkylation and glucuronic acid conjugation. Sulphoxide metabolites are mainly excreted in the urine while unchanged drug and the dealkylated form tend to be excreted in the faeces.

5.3 Preclinical safety data

Reproductive toxicity

Impaired mating performance and reduced conception rates were observed in rats treated with zuclopenthixol at doses equal to the maximum recommend human dose of 50 mg on a mg/m^2 basis.
There was no evidence of embryotoxicity or teratogenic effects in rats treated with zuclopenthixol, however adverse effects on pre-and postnatal development (i.e. increased stillbirths, reduced pup survival and delayed development of pups) was observed. 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.

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

The expiry date of the product is indicated on the packaging materials.

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

Clopixol Depot 500:
Ampoules containing 1 ml of 500 mg/ml zuclopenthixol decanoate in Triglycerides, medium-chain.

Clopixol Depot 200:
Ampoules containing 1 ml of 200 mg/ml zuclopenthixol decanoate in Triglycerides, medium-chain.

Pack sizes:
Boxes of 5 × 500 mg (1 ml ampoule), 1 × 500 mg (1 ml ampoule)
Boxes of 10 × 200 mg (1 ml ampoule)
Boxes of 1 × 200 mg (1 ml ampoule).

6.6 Special precautions for disposal

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

7. MANUFACTURER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

8. REGISTRATION HOLDER

Lundbeck Israel LTD.
11 GALGALEY HAPLADA, P.O.B. 13105, HERZLIYA 4672211

9. REGEISTRATION NUMBERS

Clopixol Depot 200 : 069 -70- 25491
Clopixol Depot 500: 047- 81- 25969

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