

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Clopixol Drops

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20 mg zuclopenthixol (as 23,64 mg zuclopenthixol dihydrochloride)

1 drop = 1 mg.

Excipients with known effect:

Ethanol.

For the full list of excipients, see Section 6.1.

### 3. PHARMACEUTICAL FORM

Oral drops, solution

Oral drops, clear, nearly colourless to yellowish solution.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Acute schizophrenia and other acute psychoses.

#### 4.2 Posology and method of administration

##### *Posology*

##### *Adults*

Dosage should be individually adjusted according to the condition of the patient. In general, small doses should be used initially and increased to the optimal effective level as rapidly as possible based on the therapeutic response. The maintenance dose can usually be given as a single dose at bedtime.

*Acute schizophrenia and other acute psychoses.* Usually 10-50 mg/day. In moderate to severe cases initially 20 mg/day increased, if necessary, by 10-20 mg every 2 to 3 days to 75 mg or more daily. Maximum dosage per single dose is 40 mg and a total of 150 mg/day.

##### *Older patients*

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

##### *Children*

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

##### *Reduced renal function*

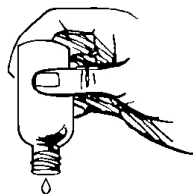
Clopixol can be given in usual doses to patients with reduced renal function.

### ***Reduced liver function***

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

### ***Method of administration***

The drops are easily administered mixed in e.g. water, orange juice or apple juice.  
Turn the bottle completely upside down. If no drops come out, tap the bottle lightly to start the flow.



## **4.3 Contraindications**

Hypersensitivity to the active ingredient or to any of the excipients, listed in section 6.1.  
Impaired consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates),  
circulatory collapse, coma.

## **4.4 Special warnings and precautions for use**

Neuroleptic malignant syndrome characterized by hyperthermia, muscle rigidity, autonomous incapacity, fluctuating consciousness and elevated levels of serum creatinine phosphokinase have been reported for antipsychotic.

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 during hospitalization.

Symptoms may persist for more than a week after oral neuroleptics are discontinued and somewhat longer when associated with the prolonged-release forms of the drug.

Zuclopenthixol must be used with caution in patients with organic brain syndrome, convulsions and advanced hepatic disease.

Insulin and glucose responses may be modified calling for adjustment of the antidiabetic therapy in diabetic patients.

Patients in long-term therapy, particularly on high doses, should be monitored carefully with regular intervals to decide whether the maintenance dosage can be decreased.

Zuclopenthixol may cause QT prolongation. Persistent QT prolongation may increase the risk of malignant arrhythmias. Therefore, zuclopenthixol should be used with caution in susceptible patients (patients with hypokalemia, hypomagnesia or patients with a genetic predisposition to arrhythmia) 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 and preventive measures undertaken.

#### Older people:

##### *Cerebrovascular*

Zuclopenthixol should be used with caution in patients with risk factors for stroke.

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.

##### *Increased Mortality in oldery people with Dementia*

Data from two large observational studies showed that older people with dementia that 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 is not licensed for the treatment of dementia-related behavioural disturbances.

##### *Excipients*

Clopixol Drops, oral drops contains 14,2% vol/vol ethyl alcohol (120 mg/ml).

Because Clopixol Drops contains ethanol it cannot be used concomitant with disulfiram or metronidazole.

As Clopixol Drops contains ethanol, caution should be taken when used for alcoholics, children, pregnant and lactating women as well of patients with epilepsy or liver diseases.

#### **4.5 Interaction with other medicinal products and other forms of interactions**

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

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

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

The co-administration of drugs known to prolong the QT interval is not recommended (see Section 4.4). Relevant classes include:

- Class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol)
- Some antipsychotics (e.g. thioridazine)
- Some macrolides (e.g. erythromycin)
- Some antihistamines (e.g. terfenadine, astemizole)
- Some quinolone antibiotics (e.g. moxifloxacin)

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

Drugs known to cause electrolyte disturbances such as thiazidediuretica (hypokalemia) and drugs known to increase the plasma concentration of zuclopenthixol should also be used with caution together with zuclopenthixol as they may increase the risk of QT prolongation and malignant arrhythmias (see Section 4.4).

Clopixol Drops, oral drops contains ethanol, see Section 4.4.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy:

Use in pregnant women should be avoided whenever possible.

Neonates exposed to antipsychotics (including zuclopenthixol) 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:

Clopixol should only be administered during lactation if considered of clinical importance, but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

Clopixol has been found in breast milk in so low concentrations that is not likely to affect the infant when administered in therapeutic doses.

The dose ingested by the infant is less than 1% of the weight related maternal daily dose (see Section 5.2).

##### 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 dysfunction 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 slightly 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 or use machines**

Clopixol may affect the ability of patients to drive and operate machinery to a less or some extent, especially at the beginning of the treatment or when the dose is increased.

#### **4.8 Undesirable effects**

The most frequently reported adverse events are dry mouth, somnolence, akathisia, hyperkinesia or hypokinesia, which are seen in more than 10% of the patients treated.

The adverse events are mostly dose dependent. The frequency and severity of the undesirable effects are most pronounced in the early phase of treatment and decline during continued treatment.

Extrapyramidal disorders may occur, especially during the early phase of treatment. In most cases these adverse events can be satisfactorily controlled by reduction of dosage and/or by using antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesia, but may aggravate the symptoms. A dose reduction is recommended or, if possible, a discontinuation of the treatment. In persistent akathisia a benzodiazepine or propranolol may be useful.

<b>Blood and lymphatic system disorders</b> Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
<b>Immune system disorders</b> Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Hypersensitivity, anaphylactic reaction.
<b>Endocrine disorders</b> Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Hyperprolactinaemia.
<b>Metabolism and nutrition disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )  Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Increased appetite, weight increase.  Decreased appetite, weight loss.  Hyperglycaemia, abnormal glucose tolerance, hyperlipidaemia.
<b>Psychiatric disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, decreased libido.  Apathy, nightmares, increased libido, confusion.
<b>Nervous system disorders</b> Very common ( $\geq 1/10$ )  Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )  Very rare ( $\leq 1/10,000$ )	Somnolence, akathisia, hyperkinesia, hypokinesia.  Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, impaired concentration, amnesia, abnormal gait.  Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disturbances, hypotonia, convulsions, migraine.  Neuroleptic malignant syndrome.
<b>Eye disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Abnormalities of visual accommodation, visual disturbances.  Oculogyration, mydriasis.
<b>Ear and labyrinth disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )	Dizziness.

Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Hyperacusis, tinnitus.
<b>Cardiac disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Tachycardia, palpitation.  QT prolongation.
<b>Vascular disorders</b> Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )  Very rare ( $\leq 1/10,000$ )	Hypotension, hot flushes.  Venous thromboembolism
<b>Respiratory, thoracic and mediastinal disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )	Blocked nose, dyspnoea.
<b>Gastrointestinal disorders</b> Very common ( $\geq 1/10$ )  Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Dry mouth.  Increased salivation, constipation, vomiting, dyspepsia, diarrhoea.  Abdominal pain, nausea, flatulence.
<b>Hepatobiliary disorders</b> Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )  Very rare ( $\leq 1/10,000$ )	Altered liver tests.  Cholestatic hepatitis, jaundice.
<b>Skin and subcutaneous tissue disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Excessive sweating, pruritus.  Rash, photosensitivity, pigmentary disturbances, seborrhoea, dermatitis, purpura.
<b>Musculoskeletal and connective tissue disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )  Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Myalgia.  Muscle rigidity, trismus, torticollis.
<b>Renal and urinary disorders</b> Common ( $\geq 1/100$ to $< 1/10$ )	Urinary disturbances, urinary retention, polyuria.
<b>Pregnancy, puerperium and perinatal conditions</b> Not known	Drug withdrawal syndrome neonatal (see 4.6)
<b>Reproductive system and breast disorders</b> Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )  Rare ( $\geq 1/10,000$ to $\leq 1/1,000$ )	Ejaculatory and erectile dysfunction, anorgasmia (women), vulvar and vaginal dryness.  Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
<b>General disorders and administration site</b>	

<b>conditions</b>	
Common ( $\geq 1/100$ to $< 1/10$ )	Asthenia, fatigue, discomfort, pain.
Uncommon ( $\geq 1/1,000$ to $\leq 1/100$ )	Thirst, hypothermia, fever.

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).

Abrupt discontinuation of zuclopenthixol may lead to withdrawal symptoms. The most common reactions are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgia, paraesthesia, insomnia, restlessness, anxiety and agitation. Patients may also experience vertigo, may feel warm/cold, respectively, and experience tremor. The symptoms usually set in 1-4 days after discontinuation and subside during 1-2 weeks.

#### 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 (movement disorders), convulsions, shock, hyperthermia/hypothermia.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when zuclopenthixol has been administered in overdose together with drugs known to affect the heart.

The highest orally administered dose of zuclopenthixol in clinical trials was 450 mg daily.

Treatment:

Treatment is symptomatic and supportive. Measures to support the respiratory and cardio-vascular 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 disorder symptoms with biperiden.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.0 Therapeutic classification**

N 05 AF 05 – Antipsychotics, thioxanthene derivatives

### **5.1 Pharmacodynamic properties**

Zuclopenthixol is a neuroleptic of the thioxanthene group.

The antipsychotic effect of neuroleptics is related to their dopamine receptor-blocking activities, but blocking of the 5-HT-receptor may also contribute.

*In vitro*, zuclopenthixol has a high affinity for both dopamine D<sub>1</sub> and D<sub>2</sub> receptors, to  $\alpha_1$ -adrenergic and 5-HT<sub>2</sub> receptors, but no affinity for cholinergic muscarinic receptors. It has a weak affinity for histamine (H<sub>1</sub>) and no  $\alpha_2$ -adrenoceptorblocking activity. *In vivo*, the affinity for D<sub>2</sub> binding sites dominates over the affinity for D<sub>1</sub> receptors.

Zuclopenthixol is a potent neuroleptic in all behavioural models for neuroleptic (dopamine receptor-blocking) activity. A correlation exists between *in vivo* test models, the affinity for D<sub>2</sub> binding sites *in vitro* and the mean daily oral dose of the antipsychotic.

Inhibition of motor activity and prolonged sleeping time induced by alcohol and barbiturates in mice indicate sedative effects in clinical use.

Like most other neuroleptics, zuclopenthixol increases the serum level of prolactin in a dose-dependent manner.

In clinical use, Clopixol is intended for the treatment of acute psychosis.

In addition to causing a significant reduction in or a complete elimination of hallucinations, delusions and thought disturbances, zuclopenthixol also has a marked effect on the accompanying symptoms such as hostility, suspiciousness, agitation and aggressiveness.

Zuclopenthixol induces a transient dose-dependent sedation. However, initial sedation is usually an advantage in the acute phase of the psychosis, since it calms the patient during the period before the antipsychotic action sets in.

Tolerance to the non-specific sedative effect develops rapidly.

## 5.2 Pharmacokinetic properties

### *Absorption*

Oral administration produces maximum serum concentration ( $T_{max}$ ) within about 4 hours. Food has no effect on absorption. Oral bioavailability: about 44 %.

### *Distribution*

Apparent volume of distribution ( $Vd$ ) <sub>$\beta$</sub> : about 20 l/kg. Plasma protein binding: 98-99 %.

### *Biostansformation*

Zuclopenthixol is mainly metabolised by sulfoxidation, side-chain N-dealkylation and conjugation with glucuronic acid. The metabolites show no neuroleptic activity. Zuclopenthixol dominates over metabolites in the brain and other tissues. Genetic polymorphism has been demonstrated.

### *Elimination*

The plasma elimination half life ( $t_{1/2\beta}$ ) is about 20 hours; systemic plasma clearance ( $Cl_s$ ) is about 0.86 l/min. Zuclopenthixol is excreted mainly with the faeces, but also to some extent with the urine (approx. 10%). Only about 0.1% is excreted unchanged with the urine.

Small amounts of zuclopenthixol are excreted in breast milk.

The milk/serum concentration ratio in women treated with oral zuclopenthixol or the decanoate was about 0.3.

### *Linearity*

The kinetics is linear. After a dose of 20 mg of zuclopenthixol once daily, the  $C_{min}$  of zuclopenthixol is about 25 nmol/l at steady state.

### *Older patients*

The pharmacokinetic parameters are largely independent of the patient's age.

### *Renal impairment*



Not studied. Based on the above elimination data, however, it is a reasonable assumption that renal impairment would not affect the serum levels of zuclopenthixol to any major degree.

#### *Hepatic impairment*

Not studied.

### **5.3 Preclinical safety data**

#### Acute toxicity

Zuclopenthixol has low acute toxicity.

#### Chronic toxicity

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

#### Reproductive toxicity

In a three generation study in rats a delay in mating was noted. Once mated there was no effect on fertility. In an experiment 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Ethanol 96%, purified water.

### **6.2 Incompatibilities**

Should only be mixed with water, orange juice or apple juice.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

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

After first opening: 6 weeks.

### **6.4 Special precautions for storage**

Before opening: Store in a refrigerator (2°C - 8°C).

After first opening: Store below 25°C.

Keep the bottle in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

Bottle (brown dropping bottle)

## **6.6 Special precautions for disposal**

No special therapeutic requirements.

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

## **7. MANUFACTURER**

H. Lundbeck A/S  
Ottiliavej 9  
2500 Valby  
Denmark

## **8. LICENSE HOLDER**

LUNDBECK ISRAEL LTD  
4 Derech Hashalom st, POB 7382, Tel Aviv

## **9. REGISTRATION NUMBER**

047-87-25488-00

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