Clopixol® Drops 20mg/ml
(zuclopenthixol)

1. NAME OF THE MEDICINAL PRODUCT

Clopixol 20 mg/ml oral drops, solution

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
Clear, nearly colourless to yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute and chronic schizophrenia and other psychoses, especially with symptoms such as hallucinations, delusions, thought disturbances as well as agitation, restlessness, hostility and aggressiveness.

Manic phase of manic-depressive illness.

Mental retardation associated with psychomotor hyperactivity, agitation, violence, and other behavioural disturbances.

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. Severe acute states of agitation. Mania.
Usually 10-50 mg/day, increased if necessary by 10 (to 20) mg every 2 to 3 days up until 100-150 mg divided in 2-3 doses per day.

Chronic schizophrenia and other chronic psychoses
Maintenance dosage usually 20-40 mg/day.

Agitation in mentally retarded patients
6-20 mg/day, if necessary increased to 25-40 mg/day.

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

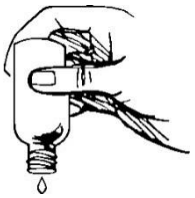
Children
Clopixol is not recommended for use in children due to lack of clinical experience.

Reduced renal function
Zuclopentixol can be given in non-adjusted doses to patients with reduced kidney-function. Zuclopentixol is eliminated renally in small extents (roughly 10%, primarily as metabolites) hence dose-adjustment for kidney patients is most likely not necessary. However, experience of treating patients with reduced kidney function is limited.

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 substance or to any of the excipients, listed in section 6.1.
- Circulatory collapse.
- Depressed CNS-function (e.g. intoxication due to alcohol, barbiturates or opioids)
- Comatose states.
- Haematological dyscrasia.
- Phaeochromocytoma.

4.4 Special warnings and precautions for use

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

The possibility of development of neuroleptic malignant syndrome (hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system) exists with any neuroleptic. Treatment: Discontinuation of the neuroleptic. Symptomatic treatment and intensive care. 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.

Dryness of mouth for long-term treatment may cause tooth and mucous damage. Teeth should be thoroughly brushed with fluorine dental-paste 2 times daily.

Abrupt discontinuation of zuclopenthixol can be associated with withdrawal symptoms. Discontinuation should thus be done gradually, see section 4.8.

QT prolongation
As neuroleptics may cause QT prolongation, caution is advised when treating patients with significant bradycardia, cardiovascular disorders, and inherent types of QT prolongation. Concomitant treatment with other antipsychotics should be avoided.

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

Elderly

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

Elderly patients are particularly susceptible to postural hypotension.

Increased Mortality in Older people with Dementia
Data from two large observational studies showed that elderly 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 is not licensed for the treatment of dementia-related behavioural disturbances.

Leukopenia, neutropenia, and agranulocytosis
Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including zuclopenthixol. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of zuclopenthixol should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 109/l) should discontinue zuclopenthixol and have their WBC followed until recovery.

Excipients
The drops contain 14.2% v/v ethyl alcohol. (120 mg/ml)

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with zuclopenthixol should be avoided:

Quinidine, a potent inhibitor of cytochrome P450 2 D6 which metabolizes most neuroleptics, should be avoided.

Codeine should be avoided as the metabolism (bioactivation of codeine) is inhibited by neuroleptics.

Bromocriptine and cabergoline are dopamine-receptor agonists and should therefore not be combined with dopamine-receptor antagonists like zuclopenthixol.

The following combinations with zuclopenthixol may require dose adjustment:

Combinations with fluoxetin, tri- and tetracyclic antidepressants, paroxetine or velafaxine may require dose adjustment as these pharmaceuticals inhibit cytochrome P450 2 D6 and slows the elimination of neuroleptics. Concurrent treatment with neuroleptics and lithium increase the risk of neurotoxic side-effects. Zuclopenthixol can counteract the effect of levodopa through dopamine-receptor blocking. Zuclopenthixol can reduce the effect of adrenergic drugs.

Zuclopenthixol can enhance the sedative effect of alcohol, barbiturates and other pharmaceuticals with inhibiting effects of the CNS.

Concurrent treatment with dopamine-receptor blocking pharmaceuticals increase the risk for extrapyramidal side-effects.

Neuroleptics can increase or decrease the effect of antihypertensive treatment.

Caution is advised during co-administration of other drugs known to increase the QT interval such as other neuroleptics, Class IA and III antiarrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium or cisaprid. Concomitant use of drugs known to cause electrolyte disturbances such as thiazidediuretics (hypokalemia) should be exercised with caution as they may increase the risk of malignant arrythmias (see section 4.4). Concomitant treatment with drugs that may increase the flupentixol blood concentration should also be exercised with caution.

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 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
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 was noted.

4.7 Effects on ability to drive and use machines

Clopixol 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 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 (≥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, 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).

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.

4.9 Overdose

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 zuclopenthixol has been taken 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 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 symptoms with biperiden.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Antipsychotics - Thioxanthene derivative.
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 D_1 and D_2 receptors, for α_1-adrenoceptors and 5-HT_2 receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H_1) receptor affinity and no α_2-adrenoceptor blocking activity.

In vivo the affinity for D_2 binding sites dominates over the affinity for D_1 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 D_2 binding sites *in vitro* and the average, daily oral antipsychotic doses.

Inhibition of locomotor activity and prolongation of alcohol- and barbiturate-induced sleeping time indicate a sedative action of zuclopenthixol.

Like most other neuroleptics zuclopenthixol increases the serum prolactin level.

Clinical efficacy and safety
In clinical use zuclopenthixol is intended for the treatment of acute and chronic psychoses and for the management of mentally handicapped patients with hyperactive and disruptive behaviour..

Besides causing a significant reduction or complete elimination of the nuclear symptoms of schizophrenia such as hallucinations, delusions and thought disturbances zuclopenthixol also has a marked effect on accompanying symptoms like hostility, suspiciousness, agitation and aggressiveness.

Zuclopenthixol induces a transient dose-dependent sedation. However, such an initial sedation is usually advantageous in the acute phase of the illness. Tolerance to the unspecific sedative effect develops rapidly.

5.2 Pharmacokinetic properties

Absorption
Oral administration results in maximum serum levels in about 4 hours. Intake with food increases C_{max} with roughly 20% and AUC with roughly 26%. This increase is not presumed to be of clinical importance. Bioavailability is about 44%.

Distribution
The apparent volume of distribution $(V_d)_\beta$ 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.

An *in vivo*-investigation has shown that one part of the metabolism is subject to genetic polymorphism for sparteine-/debrisoquine oxidation. Slow metabolisers get a prolonged half-life, lower plasma clearance and higher AUC. This should be acknowledged for treatment with zuclopenthixol, but dosing should always be individualised regarding therapeutic effect and side-effects.

Elimination
The elimination half-life ($T_{½\,\beta}$) is about 20 hours. 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. 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. is about 0.29.

Linearity
The kinetics is linear. Steady state plasma levels are achieved in about 3-5 days. The mean minimum steady state level corresponding to 20 mg zuclopenthixol once a day was about 25 nmol/l (CV 56 %). A minimum serum concentration of 7-30 nmol/l (2.8-12 ngram/ml) is suggested as guideline for maintenance treatment of schizophrenic patients with low-moderate degree of illness.

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.

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 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.

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 tumors is a common finding for D_2 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oral drops
Ethanol (96 per cent) (Alcohol Vol.% 14.2 (11.3% w/v). 120 mg/ml)
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

Before opening:
Shelf-life 18 months

After opening (in-use):
6 weeks after first opening

6.4 Special precautions for storage

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

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

After opening (in-use): Store below 25°C

Keep out of reach of children.

6.5 Nature and contents of container

Brown dropper containers of 20 ml in outer carton.

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

Product Registration Holder
Lundbeck Malaysia Sdn. Bhd.
A-05-01, Oasis Square ,
Jalan PJU 1A/7A, Ara Damansara
47301 Petaling Jaya, Selangor,
Malaysia.

8. DATE OF REVISION OF THE TEXT

June 2022