Physician prescribing Information Clopixol® Drops 20 mg/ml

SUMMARY OF PRODUCT CHARACTERISTICS

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 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.
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 should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic disease.

As described for other psychotropics zuclopenthixol 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 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. 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
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.

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

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
Combinations requiring precautions for use
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.

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 thiazidediuretica (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).

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).

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Common</th>
<th>Tachycardia, palpitations.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rare</td>
<td>Electrocardiogram QT prolonged.</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Rare</td>
<td>Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Somnolence, akathisia, hyperkinesia, hypokinesia.</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Neuroleptic malignant syndrome.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Accommodation disorder, vision abnormal.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oculogyration, mydriasis.</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Common</td>
<td>Vertigo.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hyperacusis, tinnitus.</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td>Common</td>
<td>Nasal congestion, dyspnoea.</td>
</tr>
<tr>
<td>Medical Disorders</td>
<td>Frequency</td>
<td>Clinical Features</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Dry mouth.</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Abdominal pain, nausea, flatulence.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Micturition disorder, urinary retention, polyuria.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperhidrosis, pruritus.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Hyperhidrosis, pruritus.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorder</td>
<td>Common</td>
<td>Myalgia.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Muscle rigidity, trismus, torticollis.</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Rare</td>
<td>Hyperprolactinaemia.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Increased appetite, weight increased.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Decreased appetite, weight decreased.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension, hot flush.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia, fatigue, malaise, pain.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Thirst, hypothermia, pyrexia.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Hypersensitivity, anaphylactic reaction.</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Uncommon</td>
<td>Liver function test abnormal.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Cholestatic hepatitis, jaundice.</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>Not known</td>
<td>Drug withdrawal syndrome neonatal (see 4.6)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Gynaecomastia, galactorrhea, amenorrhoea, priapism.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Apathy, nightmare, libido increased, confusional state.</td>
</tr>
</tbody>
</table>
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 D₁ and D₂ receptors, for α₁-adrenoceptors and 5-HT₂ receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H₁) receptor affinity and no α₂-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.

Inhibition of motor 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
In clinical use zuclopenthixol is intended for the treatment of acute psychoses.

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. Zuclopenthixol can be taken without regard to food intake. Oral 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. Zuclopenthixol dominates over metabolites in brain and other tissues.

Elimination
The elimination half-life ($T_{1/2\beta}$) 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. Steady state plasma levels are achieved in about 3-5 days. The mean minimum steady state level corresponding to 20 mg zuclopenthixol orally once a day was about 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 minimum (i.e. concentration measured just before administration of a dose) serum concentration of 2.8-12 ng/ml (7-30 nmol/l) is suggested as guideline for maintenance treatment of schizophrenic patients with low-moderate degree of illness.

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 oncogene 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**

2 years.

The drops are valid for at least 6 weeks after first opening. Keep the bottle in the outer carton in order to protect from light.

6.4 **Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

6.5 **Nature and contents of container**

Brown dropper containers of 10 or 20 ml in outer carton.

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. **MARKETING AUTHORIZATION HOLDER AND MANUFACTURER**

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby, Copenhagen
Denmark

8. **LICENSE HOLDER:**