

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clopixol 10 mg film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg zuclopenthixol (as 11.82 mg zuclopenthixol dihydrochloride).

Excipients with known effect

Each tablet contains 21.6 mg lactose monohydrate and 0.72 mg hydrogenated castor oil.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, light red-brown, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of psychoses, especially schizophrenia, particularly in patients who are agitated or aggressive.

4.2 Posology and method of administration

Posology

Adults

The usual dose is 20-30 mg/day, increasing as necessary to a maximum of 150 mg/day, in divided doses. The usual maintenance dose in chronic schizophrenia is 20-50 mg/day in divided doses. Lower doses may be appropriate depending on individual patient response.

Older people

Older people 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 hepatic function

Dose reduction (relative to the degree of hepatic impairment) should be considered. If possible, where assay facilities exist dosage should be adjusted according to serum levels.

Method of administration

The tablets are swallowed with water

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
- Use in children
- Use in senile confusional states

4.4 Special warnings and precautions for use

Tardive dyskinesia can occur with neuroleptic treatment. It is more common at high doses for prolonged periods but has been reported at lower dosage for short periods. The risk seems to be greater in the elderly, especially females. It has been reported that fine vermicular movements of the tongue are an early sign. It has been observed occasionally in patients receiving zuclopenthixol. The concurrent use of anticholinergic antiparkinson drugs may exacerbate this effect. The potential irreversibility and seriousness, as well as the unpredictability of the syndrome, requires especially careful assessment of the risk versus benefit, and the lowest possible dosage and duration of treatment consistent with therapeutic efficacy. Short-lived dyskinesia may occur after abrupt withdrawal of the drug.

The hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may be associated with galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea. Sexual function, including erection and ejaculation may be impaired; but increased libido has also been reported.

The possibility of development of neuroleptic malignant syndrome 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. Rare cases reported as NMS have also been received in association with zuclopenthixol. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, sweating and cardiac arrhythmia). Additional signs may include elevated creatinine, phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all neuroleptic medication, including zuclopenthixol must be discontinued. 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.

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.

Dysphagia can occur secondary to Extrapyramidal symptoms as well to Sialorrhea, Sedation and Neuroleptic malignant syndrome and may lead to life-threatening complications such as aspiration pneumonia and choking.

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

Zuclopenthixol should also be used with caution in patients who are excitable or overactive, in patients with convulsive disorders, severe atherosclerosis, severe respiratory disease and Parkinson's disease. Care should also be taken in patients with personal or family history of narrow angle glaucoma.

Administration to patients with Parkinsonism or extrapyramidal disease may induce an exacerbation of that disorder.

As described for other psychotropics zuclopenthixol may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

The general caution for use of neuroleptics in hypothyroidism, thyrotoxicosis, myasthenia gravis or prostatic hypertrophy should be observed, but there is no evidence to suggest that zuclopenthixol gives rise to any particular problem in such conditions.

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, hypomagnesaemia or family history of QT prolongation) 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 Clopixol and preventive measures undertaken

Older people

Care should also be taken in older people, particularly if frail or at risk of hypothermia, sedation, hypotension or confusion.

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 tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The tablets also contain hydrogenated castor oil which may cause stomach upset and diarrhoea.

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 and may potentiate the effects of general anaesthetics.

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.

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.

Neuroleptics may enhance the absorption of corticosteroids and digoxin, the hypotensive effects of vasodilator antihypertensive agents such as hydralazine and prolong the action of neuromuscular blocking agents.

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

As for other atypical antipsychotics, caution is advised in patients taking zuclopenthixol in concomitant use with oral anticoagulants (e.g. warfarin), and other medicinal products known to affect platelet function (e.g. phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole).

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 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 clinically significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are reversible on discontinuation.

Animal studies have shown impaired mating and reduced conception rate (see section 5.3).

4.7 Effects on ability to drive and use machines

Clopirol 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.

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.
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, extrapyramidal symptoms (see section 4.4).
	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.
	Rare	Dysphagia* (see section 4.4)
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.

**Dysphagia can occur secondary to extrapyramidal symptoms as well to sialorrhea, sedation, and neuroleptic malignant syndrome and may lead to life-threatening complications such as aspiration pneumonia and choking.*

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.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

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 α_1 -adrenoceptors and 5-HT₂ receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H₁) receptor affinity and no α_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.

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.

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)_β is about 20 l/kg.

The plasma protein binding is about 98-99 %.

Biotransformation

The metabolism of zuclopenthixol proceeds along three main routes - sulfoxidation, 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 people

The pharmacokinetic parameters are 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.

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. 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 oncogenicity 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Potato starch
Lactose monohydrate
Microcrystalline cellulose
Copovidone
Glycerol
Talc
Hydrogenated castor oil
Magnesium stearate

Coating:

Hypromellose
Macrogol 6000

Colours:

Titanium Dioxide (E171)
Red Iron Oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package and keep the bottle tightly closed in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Polypropylene or High Density Polyethylene (HDPE) containers.
Contents: 100 tablets.
The screw cap of HDPE containers contains a desiccant.
The screw cap of HDPE containers is child resistant.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7. MARKETING AUTHORISATION HOLDER

Lundbeck (Ireland) Limited
4045 Kingwood Road
Citywest Business Park
Citywest
Co.Dublin
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 0776/002/003

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st November 1982

Date of last renewal: 1st November 2007

10. DATE OF REVISION OF THE TEXT

01/2026