

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clopixol 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg zuclopenthixol (as 29.55 mg zuclopenthixol dihydrochloride).

Excipients: Each tablet contains 22 mg lactose monohydrate and 0.96 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet (tablet).

Round, biconvex 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

Route of administration

Oral.

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.

Elderly patients

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

Children

Not recommended.

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 (see 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

Extrapyramidal reactions in the form of acute dystonias (including oculogyric crisis), parkinsonian rigidity, tremor, akinesia and akathisia have been reported and may occur even at lower dosage in susceptible patients. Such effects would usually be encountered early in treatment, but delayed reactions may also occur. Antiparkinson agents should not be prescribed routinely because of the possible risk of precipitating toxic-confusional states, impairing efficacy or causing anticholinergic side-effects. They should only be given if required and their requirement reassessed at regular intervals.

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.

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, hypomagnesemia 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.

Elderly
Care should also be taken in the elderly, 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 Elderly 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.

Clopixol 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive 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 dihydrochloride 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

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with zuclopenthixol.

Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus. The newborns of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyperexcitability and have a low apgar score.

Animal embryo-foetal developmental reproduction studies on zuclopenthixol have not given evidence of an increased incidence of foetal malformations or effects on embryo viability. An animal pre and post natal study showed an increase in stillbirths, reduced pup survival and delayed development of pups at dose levels causing maternal toxicity. The potential risk for humans is unknown.

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.

Lactation

As zuclopenthixol is found in breast milk in low concentrations, breast-feeding should not be continued during therapy unless in the opinion of the physician the expected benefit to the patient outweighs the potential risk to the infant.

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 (cannot be estimated from the available data).

Cardiac disorders	Common	Tachycardia, palpitations.
	Rare	Electrocardiogram QT prolonged.
Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
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.
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.
Renal and urinary disorders	Common	Micturition disorder, urinary retention, polyuria.
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal (see 4.6).
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.
Endocrine disorders	Rare	Hyperprolactinaemia.
Metabolism and nutrition disorders	Common	Increased appetite, weight increased.
	Uncommon	Decreased appetite, weight decreased.
	Rare	Hyperglycaemia, glucose tolerance impaired,

		hyperlipidaemia.
Vascular disorders	Uncommon	Hypotension, hot flush.
	Very rare	Venous thromboembolism
General disorders and administration site conditions	Common	Asthenia, fatigue, malaise, pain.
	Uncommon	Thirst, hypothermia, pyrexia.
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction.
Hepato-biliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Cholestatic hepatitis, jaundice.
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state.

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 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

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.

Elderly patients

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 dataAcute 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

Zuclopenthixol was tested for developmental toxicity in rats and rabbits after oral administration. Under the conditions of the studies, zuclopenthixol did not induce malformations or affect embryo-foetal viability.

However, 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.

Local toxicity

Local muscle damage is seen after injection of aqueous solutions of neuroleptics, including zuclopenthixol. The muscle damage shows a much higher degree after the aqueous solutions of neuroleptics than after the oily solutions of zuclopenthixol acetate and zuclopenthixol decanoate.

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 below 25°C. Store in the original package. Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene or High Density Polyethylene (HDPE) containers.

Contents: 100 tablets

The screw cap of the HDPE containers contains a dessicant.

The screw cap of the 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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0115/005/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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