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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

CLOPIXOL TABLETS 2 mg

CLOPIXOL TABLETS 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains zuclopenthixol dihydrochloride equivalent to 2 mg or 10 mg zuclopenthixol

Contains sugar:

Each 2 mg tablet contains 17,40 mg lactose monohydrate

Each 10 mg tablet contains 21,60 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CLOPIXOL Tablets 2 mg: Round, biconvex, pale-red, film-coated tablets.

CLOPIXOL Tablets 10 mg: Round, biconvex, light red-brown, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptoms of restlessness, agitation, hostility, aggression, psychomotor excitement and other behavioural disturbances in acute and chronic schizophrenia, manic phase of bipolar affective disorder and mental retardation.

4.2 Posology and method of administration

Posology

Adults

Dosage should be individually adjusted according to the condition.

In general, small doses should be used initially and increased to the optimal effective level as rapidly as possible based on therapeutic responses. 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. In moderate to severe cases initially 20 mg/day increased, if necessary, by 10-20 mg/day every 2-3 days to 75 mg.

Chronic schizophrenia and other chronic psychoses.

Maintenance dosage usually 20-40 mg/day.

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Agitation in oligophrenic patients.

6-20 mg/day, if necessary increased to 25-40 mg daily.

Older patients

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under Composition.
Acute alcohol, barbiturate and opiate intoxications, comatose states.

4.4 Special warnings and precautions for use

Neuroleptic malignant syndrome may occur. Symptoms may be: hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system.

Treatment:

- Discontinuation of CLOPIXOL
- 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 agents.
CLOPIXOL should be used with caution in patients with convulsive disorders or advanced hepatic, renal or cardiovascular disease
CLOPIXOL may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.
Patients on long-term therapy should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

CLOPIXOL may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of cardiac dysrhythmias, resulting in an increased risk of death.
Therefore, CLOPIXOL should be used with caution in susceptible individuals (with hypokalaemia, hypomagnesaemia 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 dysrhythmia.
Concomitant treatment with other antipsychotics should be avoided (see Interactions).

Cases of venous thromboembolism (VTE) have been reported.
All possible risk factors for VTE should be identified before and during treatment with CLOPIXOL and preventive measures undertaken.

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CLOPIXOL should not be administered during pregnancy (see section 4.6).

Older people

Cerebrovascular

An approximately 3-fold increased risk of cerebrovascular ‑ accident (stroke) has 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.

CLOPIXOL 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 an 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.

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

Excipients

The tablets contain lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take CLOPIXOL.

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

4.5 Interaction with other medicines and other forms of interaction

Combinations requiring precautions for use

CLOPIXOL may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

CLOPIXOL should not be given concomitantly with guanethidine or similar acting compounds, since neuroleptics may block the antihypertensive effect of these compounds.

Concomitant use of neuroleptics and lithium increases the risk of neurotoxicity.

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of one another.

CLOPIXOL may lower the effect of levodopa and the effect of adrenergic drugs.

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

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

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Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co-administration of other agents known to significantly increase the QT interval. Co-administration of such agents should be avoided. Relevant classes include:

- class Ia and III antidysrhythmics (e.g. quinidine,amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

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

Medicines known to cause electrolyte disturbances such as thiazide diuretics (hypokalemia) and medicines known to increase the plasma concentration of zuclopentixol should also be used with caution as they may increase the risk of QT prolongation and cardiac dysrhythmias, resulting in an increased risk of death (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

CLOPIXOL should not be administered during pregnancy.

Neonates exposed to antipsychotics (including CLOPIXOL) 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.

Breastfeeding

Zuclopentixol is excreted into the breast milk. Mothers on treatment with CLOPIXOL should not breastfeed their babies.

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 were associated with a slight delay in mating. In an experiment where zuclopenthixol was administered via the diet, impaired mating performance and

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reduced conception rate was noted.

4.7 Effects on ability to drive and use machines

The ability to drive a car or operate machinery may be affected. Therefore, caution should be exercised initially, until the individual's reaction to treatment is known.

4.8 Undesirable effects

Extrapyramidal reactions may occur, Tardive dyskinesia may develop.

In the listing below a Frequent event is defined as either a very common or common event (>1/100); all other events are defined as Less frequent.

Organ class	**Frequency**	**Preferred term**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction.
Endocrine disorders	Less frequent	Hyperprolactinaemia.
Metabolism and nutritional disorders	Frequent	Increased appetite, weight increased.
	Less frequent	Decreased appetite. Weight decreased Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia
Psychiatric disorders	Frequent	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Less frequent	Apathy, nightmare, libido increased, confusional state.
Nervous system disorders	Frequent	Somnolence, akathisia, hyperkinesia, hypokinesia.
	Frequent	Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.

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	Less frequent	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine. Neuroleptic malignant syndrome.
Eye disorders	Frequent	Accommodation disorder, vision abnormal.
	Less frequent	Oculogyration, mydriasis
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Hyperacusis, tinnitus.
Cardiac disorders	Frequent	Tachycardia, palpitations.
	Less frequent	Electrocardiogram QT prolonged.
Vascular disorders	Less frequent	Hypotension, hot flush, venous thromboembolism
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Frequent	Dry mouth, salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Less frequent	Abdominal pain, nausea, flatulence.
Hepatobiliary disorders	Less frequent	Liver function test abnormal, cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, pruritus.
	Less frequent	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Frequent	Myalgia.
	Less frequent	Muscle rigidity, trismus, torticollis.
Renal and urinary disorders	Frequent	Micturition disorder, urinary retention, polyuria.

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Pregnancy, puerperium and perinatal conditions	Less frequent	Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders	Less frequent	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness, gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions	Frequent	Asthenia, fatigue, malaise, pain.
	Less frequent	Thirst, hypothermia, pyrexia.

Cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for CLOPIXOL (see section 4.4).

Abrupt discontinuation CLOPIXOL 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

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 CLOPIXOL has been taken in overdose together with drugs known to affect the Heart.

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

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Thioxanthenes

CLOPIXOL is a thioxanthene derivative with pronounced antipsychotic and specific dampening effect. The antipsychotic effect of neuroleptics is normally related to their dopamine receptor blocking effect, which seems to release a chain reaction as other transmitter systems are influenced as well.

The bioavailability after oral administration is 25-40%. Maximum serum concentration is reached after about 4 hours. Highly significant correlations exist between the dose and the area under the serum concentration curves. CLOPIXOL is distributed in the organism in the same way as seen for other neuroleptics with the highest concentrations of drug and metabolites in liver, lung, intestines and kidneys and lower concentrations in heart, spleen and brain. Autoradiographic studies in mice show that small amounts of radioactive labelled drug and/or metabolites cross the placental barrier and that some radioactivity is excreted with milk. The metabolism proceeds along three main routes - sulphoxidation, side chain N - dealkylation and glucuronic acid conjugation. The metabolites are not psychopharmacologically active. The biological half-life in humans is about 20 hours. The elimination proceeds mainly with fecal excretion being 8-11 times urinary excretion in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients Tablet core:

Copovidone, glycerol 85%, hydrogenated castor oil, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potato starch, talc.

Coating:

Hypromellose 5,
Macrogol 6000

Colours:

Red iron oxide (E 172),
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

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6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from light.

Keep out of reach of children.

6.5 Nature and contents of the container

100 tablets packed in a 60 ml white plastic container with a child resistant, tamper evident closure and with a white desiccant gel capsule in the closure, supplied in a carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

H. Lundbeck (Pty) Ltd
Office A1002, First Floor, Knightsbridge
33 Sloane Street, Bryanston
2190
South Africa

8. REGISTRATION NUMBERS

CLOPIXOL Tablets 2 mg: T/2.6.5/180

CLOPIXOL Tablets 10 mg: T/2.6.5/181

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 June 1991

10. DATE OF REVISION OF THE TEXT

03 November 2023