1 NAME OF THE MEDICINAL PRODUCT

Clopixol 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg zuclopenthixol (as dihydrochloride).

Excipients with known effect:

Lactose monohydrate
Hydrogenated castor oil.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Round, biconvex, pale red, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of psychoses, especially schizophrenia.

4.2 Posology and method of administration

Posology

Adults

The dosage range is 4-150 mg/day in divided doses. The usual initial dose is 20-30 mg/day (sometimes with higher dosage requirements in acute cases), increasing as necessary. The usual maintenance dose is 20-50 mg/day.

Maximum dosage per single dose is 40 mg.

When transferring patients from oral to depot antipsychotic treatment, the oral medication should not be discontinued immediately, but gradually withdrawn over a period of several days after administering the first injection.

Older patients

In accordance with standard medical practice, initial dosage may need to be reduced to a quarter or half the normal starting dose in the frail or older patients.

Paediatic population

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

Patients with renal impairment

Clopixol can be given in usual doses to patients with reduced renal function. Where there is renal failure dosage should be reduced to half the normal dosage.

Patients with hepatic impairment

Use with caution in patients with liver disease (see section 4.4). Patients with compromised hepatic function should receive half the recommended dosages. Serum-level monitoring is advised

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.

4.4 Special warnings and precautions for use

Caution should be exercised in patients having: liver disease; cardiac disease, or arrhythmias; severe respiratory disease; renal failure; epilepsy (and conditions predisposing to epilepsy, e.g. alcohol withdrawal or brain damage); Parkinson's disease; narrow angle glaucoma; prostatic hypertrophy; hypothyroidism; hyperthyroidism; myasthenia gravis; phaeochromocytoma and patients who have shown hypersensitivity to thioxanthenes or other antipsychotics.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

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, convulsions or advanced hepatic disease.

Blood dyscrasias have been reported rarely. Blood counts should be carried out if a patient develops signs of persistent infection.

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 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 arrhythmia.

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.

Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

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

Older people

Older people require close supervision because they are especially prone to experience such adverse effects as sedation, hypotension, confusion, and temperature changes.

Cerebrovascular

An approximately 3-fold increased risk of cerebrovascular adverse events 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.

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.

Clopixol tablets are 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.

This medicinal product contains hydrogenated castor oil, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antipsychotics, zuclopenthixol enhances the response to alcohol, the effects of barbiturates and other CNS depressants.

Zuclopenthixol may potentiate the effects of general anaesthetics and anticoagulants and prolong the action of neuromuscular blocking agents.

The anticholinergic effects of atropine or other drugs with anticholinergic properties may be increased.

Concomitant use of drugs such as metoclopramide, piperazine or antiparkinson drugs may increase the risk of extrapyramidal effects such as tardive dyskinesia.

Combined use of antipsychotics and lithium or sibutramine has been associated with an increased risk of neurotoxicity.

Antipsychotics may enhance the cardiac depressant effects of quinidine; the absorption of corticosteroids and digoxin.

The hypotensive effect of vasodilator antihypertensive agents such as hydralazine and α-blockers (e.g. doxazosin), or methyl-dopa may be enhanced.

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
- some quinolone antibiotics (e.g. 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 thiazidediuretics (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).

Antipsychotics may antagonise the effects of adrenaline and other sympathomimetic agents, and reverse the antihypertensive effects of guanethidine and similar adrenergic-blocking agents.

Antipsychotics may also impair the effect of levodopa, adrenergic drugs and anticonvulsants.

The metabolism of tricyclic antidepressants may be inhibited and the control of diabetes may be impaired.

Since zuclopenthixol is partly metabolised by CYP2D6 concomitant use of drugs known to inhibit this enzyme may lead to to higher than expected plasma concentrations of zuclopenthixol, increasing the risk of adverse effects and cardiotoxicity.

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.

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

Zuclopenthixol is a sedative drug.

Alertness may be impaired, especially at the start of treatment, or following the consumption of alcohol; patients should be warned of this risk and advised not to drive or operate machinery until their susceptibility is known.

Patients should not drive if they have blurred vision.

4.8 Undesirable effects

The majority of undesirable effects are 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 it. Reduction in dosage or, if possible, discontinuation of zuclopenthixol therapy is recommended. In persistent akathisia a benzodiazepine or propranolol may be useful.

Blood and lymphatic system disorders	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
Immune system disorders	Hypersensitivity, anaphylactic reaction.
Endocrine disorders	Hyperprolactinaemia.
Metabolism and nutrition disorders	Increased appetite, weight increased.
	Decreased appetite, weight decreased.
	Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.

Psychiatric disorders	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Apathy, nightmare, libido increased, confusional state.
Nervous system disorders	Somnolence, akathisia, hyperkinesia, hypokinesia.
	Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.
	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine.
	Neuroleptic malignant syndrome.
Eye disorders	Accommodation disorder, vision abnormal.
	Oculogyration, mydriasis.
Ear and labyrinth disorders	Vertigo.
	Hyperacusis, tinnitus.
Cardiac disorders	Tachycardia, palpitations.
	Electrocardiogram QT prolonged.
Vascular disorders	Hypotension, hot flush.
	Venous thromboembolism
Respiratory, thoracic and medistianal disorders	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Dry mouth.
	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Abdominal pain, nausea, flatulence.
Hepato-biliary disorders	Liver function test abnormal.
	Cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Hyperhidrosis, pruritus.
	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Myalgia.
	Muscle rigidity, trismus, torticollis.
Renal and urinary disorders	Micturition disorder, urinary retention, polyuria.
Pregnancy, puerperium and	Drug withdrawal syndrome neonatal

perinatal conditions	(see 4.6)
Reproductive system and breast disorders	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions	Asthenia, fatigue, malaise, pain.
	Thirst, injection site reaction, 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).

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Overdosage may cause somnolence, or even coma, extrapyramidal symptoms, convulsions, hypotension, shock, hyper-or hypothermia. Treatment is symptomatic and supportive, with measures aimed at supporting the respiratory and cardiovascular systems. The following specific measures may be employed if required.

- anticholinergic antiparkinson drugs if extrapyramidal symptoms occur.
- sedation (with benzodiazepines) in the unlikely event of agitation or excitement or convulsions.
- noradrenaline in saline intravenous drip if the patient is in shock. Adrenaline must not be given.
- Gastric lavage should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Neuroleptics (antipsychotics), ATC code: N05AF05

The action of zuclopenthixol, as with other antipsychotics is mediated through dopamine receptor blockage. Zuclopenthixol has a high affinity for D1 and D2 receptors and activity has been demonstrated in standard animal models used to assess antipsychotic action. Serotonergic blocking properties, a high affinity for alpha-adrenoreceptors and slight antihistamine properties have been observed.

5.2 Pharmacokinetic properties

Zuclopenthixol given orally in man is relatively quickly absorbed and maximum serum concentrations are reached in 3-6 hours. There is good correlation between the dose of zuclopenthixol and the concentrations achieved in serum. The biological half-life in man is about one day. Zuclopenthixol is distributed in the liver, lungs, intestines and kidney, with somewhat lower concentration in the brain. Small amounts of drug or metabolites cross the placenta and are excreted in milk.

Zuclopenthixol is metabolised by sulphoxidation, N-Dealkylation and glucuronic acid conjugation.

The faecal route of excretion predominates and mostly unchanged zuclopenthixol and N-dealkylated metabolite are excreted in this way.

5.3 Preclinical safety data

Reproductive toxicity

Impaired mating performance and reduced conception rates were observed in rats treated with zuclopenthixol at doses equal to the maximum recommend human dose of 50 mg on a mg/m^2 basis.

There was no evidence of embryotoxicity or teratogenic effects in rats treated with zuclopenthixol, however adverse effects on pre-and postnatal development (i.e. increased stillbirths, reduced pup survival and delayed development of pups) was observed. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch, Lactose, Microcrystalline cellulose, Copolyvidone, Glycerol, Talc, Caster Oil, hydrogenated, Magnesium Stearate, Methylhydroxypropyl Cellulose, Macrogol, Titanium Dioxide (E171) and Red Iron Oxide (E172).

6.2 Incompatibilities

None known.

6.3 Shelf life

Clopixol Tablets 2 mg are stable for 2 years. Each container has an expiry date.

6.4 Special precautions for storage

Store below 25□C.

Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

Grey polypropylene container with desiccant capsule

or

Glass bottle

or

White HDPE container with LDPE twist-off cap including desiccant

Pack size: 100 tablets

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Lundbeck Limited

Iveco House,

Station Road,

Watford,

Hertfordshire,

WD17 1ET,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

2 mg tablets: PL 00458/0027

10 mg tablets: PL 00458/0028

25 mg tablets: PL 00458/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/07/2008

10 DATE OF REVISION OF THE TEXT

29/06/2022