SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clopixol 2 mg tablets
Clopixol 10 mg tablets
Clopixol 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopixol 2 mg	Each tablet contains 2 mg zuclopenthixol (as 2.364 mg zuclopenthixol dihydrochloride)
Clopixol 10 mg	Each tablet contains 10 mg zuclopenthixol (as 11.82 mg zuclopenthixol dihydrochloride)
Clopixol 25 mg	Each tablet contains 25 mg zuclopenthixol (as 29.55 mg zuclopenthixol dihydrochloride)

Excipients with known effect:
Clopixol 2 mg contains 17.4 mg lactose monohydrate.
Clopixol 10 mg contains 21.6 mg lactose monohydrate.
Clopixol 25 mg contains 22.0 mg lactose monohydrate.

Hydrogenated castor oil

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablets, film-coated

Description of the tablets:

2 mg:	Round, biconvex, pale red, film-coated tablet.
10 mg:	Round, biconvex, light red-brown film-coated tablet.
25 mg:	Round, biconvex, red-brown, film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute schizophrenia, 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 tablets are swallowed with water.

4.3 Contraindications
Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
Impaired consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), circulatory collapse, coma.

4.4 Special warnings and precautions for use
Neuroleptic malignant syndrome
Neuroleptic malignant syndrome characterized by hyperthermia, muscle rigidity, autonomous incapacity, fluctuating consciousness and elevated levels of serum creatinine phosphokinase have been reported for neuroleptics.
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 during hospitalization.

Symptoms may persist for more than a week after oral neuroleptics are discontinued and somewhat longer when associated with the prolonged-release forms of the drug.

Zuclopenthixol must be used with caution in patients with organic brain syndrome, convulsions and advanced hepatic disease.

Insulin and glucose responses may be modified calling for adjustment of the antidiabetic therapy in diabetic patients.

Patients in long-term therapy, particularly on high doses, should be monitored carefully with regular intervals to decide whether the maintenance dosage can be decreased.

Zuclopenthixol may cause QT prolongation. Persistent QT prolongation may increase the risk of malignant arrhythmias. Therefore, zuclopenthixol should be used with caution in susceptible patients (patients with hypokalemia, hypomagnesia or patients with a genetic predisposition to arrhythmia) 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 antispsychotics 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
Zuclopenthixol should be used with caution in patients with risk factors for stroke.
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.

Increased Mortality in Older people with Dementia
Data from two large observational studies showed that older people with dementia that 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 contain hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interactions

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.

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

The co-administration of drugs known to prolong the QT interval is not recommended (see Section 4.4). Relevant classes include:
- Class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol)
- Some antipsychotics (e.g. thioridazine)
- Some macrolides (e.g. erythromycin)
- Some antihistamines (e.g. terfenadine, astemizole)
- Some quinolone antibiotics (e.g. moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly prolong 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 together with zuclopenthixol as they may increase the risk of QT prolongation and malignant arrhythmias (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Use in pregnant women should be avoided whenever possible.

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.

Animal studies have shown reproductive toxicity (see section 5.3).

Breast-feeding:
Clopixol should only be administered during lactation if considered of clinical importance, but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

Clopixol has been found in breast milk in so low concentrations that is not likely to affect the infant when administered in therapeutic doses.
The dose ingested by the infant is less than 1% of the weight related maternal daily dose (see Section 5.2).

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 dysfunction 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 slightly 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 or use machines

Clopixol may affect the ability of patients to drive or operate machinery to a less or some extent, especially at the beginning of the treatment or when the dose is increased.

4.8 Undesirable effects

The most frequently reported adverse events are dry mouth, somnolence, akathisia, hyperkinesia or hypokinesia, which are seen in more than 10% of the patients treated.

The adverse events are mostly dose dependent. The frequency and severity of the undesirable effects are most pronounced in the early phase of treatment and decline during continued treatment.

Extrapyramidal disorders may occur, especially during the early phase of treatment. In most cases these adverse events can be satisfactorily controlled by reduction of dosage and/or by using antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesia, but may aggravate the symptoms. A dose reduction is recommended or, if possible, a discontinuation of the treatment. In persistent akathisia a benzodiazepine or propranolol may be useful.

Blood and lymphatic system disorders Rare (≥1/10,000 to ≤1/1,000)	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
Immune system disorders Rare (≥1/10,000 to ≤1/1,000)	Hypersensitivity, anaphylactic reaction.
Endocrine disorders Rare (≥1/10,000 to ≤1/1,000)	Hyperprolactinaemia.
Metabolism and nutrition disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100) Rare (≥1/10,000 to ≤1/1,000)	Increased appetite, weight increase. Decreased appetite, weight loss. Hyperglycaemia, abnormal glucose tolerance, hyperlipidaemia.
Psychiatric disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, decreased libido. Apathy, nightmares, increased libido, confusion.
Nervous system disorders Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100) Very rare (≤1/10,000)	Somnolence, akathisia, hyperkinesia, hypokinesia. Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, impaired concentration, amnesia, abnormal gait. Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disturbances, hypotonia, convulsions, migraine. Neuroleptic malignant syndrome.
Eye disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Abnormalities of visual accommodation, visual disturbances. Oculogyration, mydriasis.
Ear and labyrinth disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Dizziness. Hyperacusis, tinnitus.

Cardiac disorders Common (≥1/100 to <1/10) Rare (≥1/10,000 to ≤1/1,000)	Tachycardia, palpitation. QT prolongation.
Vascular disorders Uncommon (≥1/1,000 to ≤1/100) Very rare (≤1/10,000)	Hypotension, hot flushes. Venous thromboembolism
Respiratory, thoracic and mediastinal disorders Common (≥1/100 to <1/10)	Blocked nose, dyspnoea.
Gastrointestinal disorders Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Dry mouth. Increased salivation, constipation, vomiting, dyspepsia, diarrhoea. Abdominal pain, nausea, flatulence.
Hepatobiliary disorders Uncommon (≥1/1,000 to ≤1/100) Very rare (≤1/10,000)	Altered liver tests. Cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Excessive sweating, pruritus. Rash, photosensitivity, pigmentary disturbances, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to ≤1/100)	Myalgia. Muscle rigidity, trismus, torticollis.
Renal and urinary disorders Common (≥1/100 to <1/10)	Urinary disturbances, urinary retention, polyuria.
Pregnancy, puerperium and perinatal conditions Not known	Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders Uncommon (≥1/1,000 to ≤1/100) Rare (≥1/10,000 to ≤1/1,000)	Ejaculatory and erectile dysfunction, anorgasmia (women), vulvar and vaginal dryness. Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions Common (≥1/100 to <1/10)	Asthenia, fatigue, discomfort, pain.

Uncommon (≥1/1,000 to ≤1/100)	Thirst, hypothermia, fever.

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 lead to withdrawal symptoms. The most common reactions are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgia, paraesthesia, insomnia, restlessness, anxiety and agitation. Patients may also experience vertigo, may feel warm/cold respectively, and experience tremor. The symptoms usually set in 1-4 days after discontinuation and subside during 1-2 weeks.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose
Symptoms:
Somnolence, coma, extrapyramidal symptoms (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 administered 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 cardio-vascular 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 disorder symptoms with biperiden.

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification
N 05 AF 05 – Antipsychotics, thioxanthene derivatives

5.1 Pharmacodynamic properties
Zuclopenthixol is a neuroleptic of the thioxanthene group.
The antipsychotic effect of neuroleptics is related to their dopamine receptor-blocking activities, but blocking of the 5-HT-receptor may also contribute.

In vitro, zuclopenthixol has a high affinity for both dopamine D_1 and D_2 receptors, to α_1-adrenergic and 5-HT_2 receptors, but no affinity for cholinergic muscarinic receptors. It has a weak affinity for histamine (H_1) and no α_2-adrenoceptorblocking activity. *In vivo*, the affinity for D_2 binding sites dominates over the affinity for D_1 receptors.

Zuclopenthixol is a potent neuroleptic in all behavioural models for neuroleptic (dopamine receptor-blocking) activity. A correlation exists between *in vivo* test models, the affinity for D_2 binding sites *in vitro* and the mean daily oral dose of the antipsychotic.

Inhibition of motor activity and prolonged sleeping time induced by alcohol and barbiturates in mice indicate sedative effects in clinical use.

Like most other neuroleptics, zuclopenthixol increases the serum level of prolactin in a dose-dependent manner.
In clinical use, Clopixol is intended for the treatment of acute psychosis.

In addition to causing a significant reduction in or a complete elimination of hallucinations, delusions and thought disturbances, zuclopenthixol also has a marked effect on the accompanying symptoms such as hostility, suspiciousness, agitation and aggressiveness.

Zuclopenthixol induces a transient dose-dependent sedation. However, initial sedation is usually an advantage in the acute phase of the psychosis, since it calms the patient during the period before the antipsychotic action sets in.
Tolerance to the non-specific sedative effect develops rapidly.

5.2 Pharmacokinetic properties

Absorption
Oral administration produces maximum serum concentration (T_{max}) within about 4 hours. Food has no effect on absorption. Oral bioavailability: about 44 %.

Distribution
Apparent volume of distribution$(Vd)_{\beta}$: about 20 l/kg. Plasma protein binding: 98-99 %.

Biotransformation
Zuclopenthixol is mainly metabolised by sulfoxidation, side-chain N-dealkylation and conjugation with glucuronic acid. The metabolites show no neuroleptic activity. Zuclopenthixol dominates over metabolites in the brain and other tissues. Genetic polymorphism has been demonstrated.

Elimination
The plasma elimination half life ($t_{½\,\beta}$) is about 20 hours; systemic plasma clearance (Cl_s) is about 0.86 l/min. Zuclopenthixol is excreted mainly with the faeces, but also to some extent with the urine (approx. 10%). Only about 0.1% is excreted unchanged with the urine.

Small amounts of zuclopenthixol are excreted in breast milk.
The milk/serum concentration ratio in women treated with oral zuclopenthixol or the decanoate was about 0.3.

Linearity
The kinetics is linear. After a dose of 20 mg of zuclopenthixol once daily, the C_{min} of zuclopenthixol is about 25 nmol/l at steady state.

Older patients
The pharmacokinetic parameters are largely independent of the patient's age.

Renal impairment
Not studied. Based on the above elimination data, however, it is a reasonable assumption that renal impairment would not affect the serum levels of zuclopenthixol to any major degree.

Hepatic impairment
Not studied.

5.3 Preclinical safety data

Acute toxicity

Zuclopenthixol has low acute toxicity.

Chronic toxicity

In chronic toxicity studies, there were no findings of importance 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Potato starch, lactose monohydrate, microcrystalline cellulose, copovidone, glycerol (85 per cent), talc, hydrogenated castor oil, magnesium stearate.

Coating:

Hypromellose 5, macrogol 6000.

Colours:

Titanium dioxide (E171), red iron oxide (E172).

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

2 mg: Store below 25ºC, in original container in order to protect from light.

10 mg, 25 mg : Store below 25ºC.

6.5 Nature and contents of container

50 and 100 tablets in HDPE containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MANUFACTURER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

8. LICENSE HOLDER

LUNDBECK ISRAEL LTD

4 Derech Hashalom st, POB 7382, Tel Aviv

9. REGISTRATION NUMBERS

Clopixol 2 mg tablets: 047-84-25485
Clopixol 10 mg tablets: 047-86-25486
Clopixol 25 mg tablets: 047-85-25487