AUSTRALIAN PRODUCT INFORMATION

CLOPIXOL® (ZUCLOPENTHIXOL HYDROCHLORIDE) FILM-COATED TABLETS

CLOPIXOL® ACUPHASE (ZUCLOPENTHIXOL ACETATE) INJECTION

CLOPIXOL® DEPOT (ZUCLOPENTHIXOL DECANOATE) INJECTION

1 NAME OF THE MEDICINE

Clopixol® Tablets	Clopixol® Acuphase Injection	Clopixol® Depot Injection
Zuclopenthixol hydrochloride	Zuclopenthixol acetate	Zuclopenthixol decanoate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopixol tablets
Film-coated tablets containing 10 mg zuclopenthixol as zuclopenthixol hydrochloride.

Clopixol Acuphase injection
The 1 mL solution for injection contains 50 mg zuclopenthixol acetate equivalent to 45.25 mg zuclopenthixol.

The 2 mL solution for injection containing 100 mg zuclopenthixol acetate equivalent to 90.50 mg zuclopenthixol.

Clopixol Depot injection
The 1 ml solution for injection contains 200 mg zuclopenthixol decanoate equivalent to 144.4 mg zuclopenthixol.

Excipients with known effect in the tablets: sugars as lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Clopixol tablets
Film-coated tablets. Clopixol 10 mg tablets are light red brown, round biconvex film-coated tablets.

Clopixol Acuphase injection
Solution for injection. Clopixol Acuphase injection presents as a clear, yellowish oil.

Clopixol Depot injection
Solution for injection. Clopixol Depot injection presents as a clear, yellowish oil.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopixol tablets

Acute and chronic schizophrenia and other psychoses, especially those with symptoms such as hallucinations, delusions, thought disturbances, agitation, restlessness, hostility or aggressiveness.

Manic phase of manic depressive illness.

Clopixol Acuphase injection

Initial treatment of acute psychoses, mania and exacerbation of chronic psychoses.

Clopixol Depot injection

Maintenance treatment. May be an advantage in the treatment of noncompliant patients.

4.2 Dose and method of administration

Adults

Clopixol tablets

Dosage should be adjusted individually. In general, small doses should be used initially and increased to the optimal effective level as rapidly as possible, based on the response. The maintenance dose can usually be given as a single dose at bedtime.

Concomitant intake of food enhances the bioavailability by approximately 20% of Clopixol tablets without influencing its absorption rate. C_{max}, t_{max} and elimination half-life ($t_{½}$) are not altered. The postulated mechanism for this effect is that food reduces the presystemic clearance of zuclopenthixol. This effect is of doubtful clinical relevance and it does not appear that Clopixol tablets need to be given with regard to meals.

Acute schizophrenia and other acute psychoses; severe, acute states of agitation; mania

Usually 10 - 50 mg/day orally. In moderate to severe cases, initially 20 mg/day increasing, if necessary, by 10 - 20 mg every 2 - 3 days to 75 mg or more daily.

Chronic schizophrenia and other chronic psychoses

The usual maintenance dose is 20 - 40 mg/day orally.

Clopixol Acuphase injection

Dosage should be individually adjusted according to the patient's condition. Clopixol Acuphase is administered by intramuscular injection. Local tolerability is good.

The dose range is usually 50 - 150 mg (1 - 3 mL) i.m., repeated if necessary, preferably at intervals of 2 to 3 days. In some cases, an additional injection may be needed 24 to 48 hours following the first injection.

Clopixol Acuphase is not intended for long-term use and the duration of treatment should not be more than 2 weeks. The maximum accumulated dosage in a course should not exceed 400 mg and the total number of injections should not exceed 4.

In the maintenance therapy, treatment should be continued with oral Clopixol or Clopixol Depot i.m. according to the following guidelines:

1. Change to oral Clopixol 2 to 3 days after the last injection of Clopixol Acuphase:

   If the patient has been treated with 100 mg Clopixol Acuphase, oral treatment should be started at a dosage of about 40 mg daily, possibly in divided dosages. If necessary the dose can be further increased by 10 - 20 mg every 2 to 3 days up to 75 mg or more.

2. Change to maintenance treatment with Clopixol Depot:

   Concomitantly with the last injection of Clopixol Acuphase, 200 - 400 mg (1 – 2 mL) of Clopixol Depot should be given intramuscularly and repeated every second week. Higher doses or shorter intervals may be needed.

Clopixol Depot injection

The usual maintenance dose is 200 - 400 mg (1 - 2 mL) every second to fourth week. A few patients may need higher doses or shorter intervals between doses.

When changing medication from oral Clopixol or Clopixol Acuphase to maintenance treatment with Clopixol Depot, the following guidelines should be used:

1. Change from oral Clopixol to Clopixol Depot i.m.:

   mg Clopixol orally daily x 8 = mg Clopixol Depot i.m. every second week.

   Oral Clopixol should be continued during the first week after the first injection but in diminishing dosage.

2. Change from Clopixol Acuphase i.m. to Clopixol Depot i.m.:

Concomitantly with the last injection of Clopixol Acuphase, 200 - 400 mg (1 – 2 mL) of Clopixol Depot should be given intramuscularly and repeated every second week. Higher doses or shorter intervals between injections may be needed.

Elderly patients
The dosage may need to be reduced in elderly patients.

Children
Since the safety and efficacy of Clopixol in children have not been established, its use is not recommended in this age group.

Reduced hepatic function
Clopixol should be used with caution in patients with mild to moderate liver disease (see Section 4.4 Special warnings and precautions for use).

Reduced renal function
Since approximately 10% of a zuclopenthixol dose is excreted via the renal system, patients with renal dysfunction may require dosage adjustment during long-term treatment (see Section 4.4 Special warnings and precautions for use).

Clinical particulars
If a rapid and pronounced reduction in psychotic symptoms is required, it is recommended to start treatment parenterally with Clopixol Acuphase 50 mg/mL (zuclopenthixol acetate). Clopixol Acuphase has a duration of action of 2 to 3 days and 1 or 2 injections are usually sufficient prior to the introduction of maintenance treatment with Clopixol tablets or Clopixol Depot injection solution (see Section 4.2 Dose and method of administration).

In the maintenance treatment of psychotic patients, particularly where compliance with oral medication is a problem, it may be beneficial to continue treatment with Clopixol Depot 200 mg/mL (zuclopenthixol decanoate) which is administered at intervals of 2 – 4 weeks.

In addition to its antipsychotic effect, zuclopenthixol also has a non-specific sedative effect on accompanying symptoms such as agitation, restlessness, hostility or aggression.

Zuclopenthixol induces dose-dependent sedation. Tolerance to the non-specific sedative effect develops rapidly. Significant sedation occurs within 2 hours of injection of Clopixol Acuphase, reaching a maximum after 8 hours then declining to a low level, despite repeated injection.

Instructions to patients

1. Ambulant patients should be warned not to drive or operate machinery during the use of Clopixol.

2. Patients should be forewarned and reassured concerning the possible occurrence of extrapyramidal symptoms.

3. Patients should be instructed to report any soreness of the mouth, gums, throat or other symptoms which may indicate suppression of the immune system.

4.3 Contraindications

Known hypersensitivity to the thioxanthenes. The possibility of cross-sensitivity between the thioxanthenes and phenothiazine derivatives should be kept in mind.

Known hypersensitivity to any of the excipients of the particular Clopixol presentation (see Section 2 Qualitative and quantitative composition).

Acute alcohol, barbiturate or opiate intoxication.

Circulatory collapse, depressed level of consciousness due to any cause, coma, suspected or established subcortical brain damage.

Blood dyscrasias.

Phaeochromocytoma.

Leukopenia and/or previous agranulocytosis.

4.4 Special warnings and precautions for use

Identified precautions

Neuroleptic Malignant Syndrome

A potentially fatal syndrome called neuroleptic malignant syndrome (NMS) has been reported on occasion with antipsychotic drugs. The syndrome is characterised by muscle rigidity, fever, hyperthermia, altered consciousness and autonomic instability (e.g. tachycardia, labile blood pressure, profuse sweating, dyspnoea). The management of neuroleptic malignant syndrome should include immediate discontinuation of antipsychotic drugs, intensive monitoring of symptoms and treatment of any associated medical problems. 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.

Initiation of therapy

Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Therefore, the evaluation of tolerance and response, and establishment of adequate maintenance therapy require careful stabilisation of each patient under continuous, close medical observation and supervision.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany therapy.

Extrapyramidal Reactions

Extrapyramidal reactions may occur, especially in the first few days after an injection and in early phase of treatment. Similarly, these may occur with the tablets especially in the early

days 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
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.

Dyskinesia
The possibility of the development of irreversible dyskinesia should be borne in mind when patients are on prolonged therapy with Clopixol.

Photosensitivity reactions
Photosensitivity reactions have been reported with related drugs.

Ophthalmological
Pigmentary retinopathy and lenticular and corneal deposits have been reported with related drugs. Lens opacity has been reported rarely with zuclopenthixol.

Anaphylactoid reactions
The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

Psychoses with apathy or withdrawal
Clopixol is unsuitable for patients whose psychoses are accompanied by features of apathy or withdrawal.

Parkinsonism
Clopixol should be used with caution in patients with Parkinsonism.

Arteriosclerosis
Clopixol should be used with caution in patients with severe arteriosclerosis.

Organic brain syndrome
Like other neuroleptics, Clopixol should be used with caution in patients with organic brain syndrome.

Stroke
An approximate 3-fold increase in 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. Therefore, zuclopenthixol should be used with caution in patients with risk factors for stroke.

Cerebrovascular insufficiency
Patients who have cerebrovascular insufficiency should be closely monitored during treatment with Clopixol.

Convulsions
Clopixol should be used with caution in patients with a history of convulsions since it may lower the convulsive threshold.

Anticholinergic effects
Although its anticholinergic properties are weak, zuclopenthixol should be used with caution in patients who are known to have, or suspected of having, glaucoma; those who might be exposed to extreme heat or organo-phosphorus insecticides, and those who are receiving atropine or related drugs. Paralytic ileus has occasionally been reported (particularly in the elderly) when several drugs with anticholinergic effects have been used simultaneously.

White blood cell disorders
Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including zuclopenthixol.

Long-acting depot antipsychotics should be used with caution in combination with other medicines known to have a myelosuppressive potential, as these cannot rapidly be removed from the body in conditions where this may be required.

Laboratory tests required
Blood dyscrasias and liver damage have been reported with this class of drugs (see Section 4.8 Adverse Effects (Undesirable effects)). Therefore, routine blood counts and hepatic function tests are advisable, particularly during the first months of therapy. Should either of these disorders occur, supportive treatment should be instituted and administration of the drug ceased.

Cellular depression
If any soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Cardiac disorders
Caution should be observed when using a drug of this category in patients who have advanced cardiovascular disease or those who may have a propensity for development of cardiac conduction defects.

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), recent acute myocardial infarction, uncompensated heart failure, or cardiac

arrhythmia. Concomitant treatment with other antipsychotics should be avoided (see Section 4.5 Interactions with other medicines and other forms of interactions).

Venous thromboembolism (VTE)

cases 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.

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.

Zuclopenthixol is not approved for the treatment of dementia-related behavioural disturbances.

Diabetes

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

Surgery

Patients on large doses of zuclopenthixol who are undergoing surgery should be carefully observed for possible hypotensive phenomena. Dosages of anaesthetic or central nervous system depressant drugs may need to be reduced.

Monitoring

To lessen the likelihood of adverse reactions related to drug accumulation, patients on long-term therapy or receiving high doses of zuclopenthixol should be monitored carefully and evaluated periodically in order to determine whether the maintenance dosage can be lowered or drug therapy discontinued.

Antiemetic effect

The antiemetic effect observed with zuclopenthixol in animal studies may also occur in man. Therefore, the drug may mask signs of toxicity due to overdosage of other drugs, or it may mask symptoms of disease such as brain tumour or intestinal obstruction.

Sleep apnoea

No cases of sleep apnoea clearly attributed to zuclopenthixol have been reported and no epidemiology studies can substantiate this. However, sleep apnoea and related disorders have been reported in patients treated with other atypical antipsychotic medications, with or without prior history of sleep apnoea, and in patients with or without concomitant weight-gain. In patients who have a history of, or are at risk for, sleep apnoea, or who are concomitantly using central nervous system depressants, zuclopenthixol should be used with caution.

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine. They also contain hydrogenated castor oil which may cause stomach upset and diarrhoea.

Use in hepatic impairment
Clopixol should be used with caution in patients with liver disease. Patients with compromised hepatic function should be given half the recommended dose and serum levels monitored (see Section 4.2 Dose and method of administration).

Use in renal impairment
Since only about 0.1% of a zuclopenthixol dose is excreted unchanged via the renal system, patients with mild to moderate renal dysfunction can receive Clopixol in the usual dosage. In patients with renal failure the dosage should be reduced to half the usual dose and close monitoring instituted.

Use in the elderly
See Section 4.2 Dose and method of administration..

Paediatric use
The safety and efficacy of Clopixol in children have not been established, therefore its use cannot be recommended in this age group.

Effects on laboratory tests
Transient slight alterations in liver function tests have infrequently been reported.

4.5 Interactions with other medicines and other forms of interactions

Tricyclic antidepressants - Tricyclic antidepressants and classical neuroleptics mutually inhibit the metabolism of each other.

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

Alcohol, other CNS depressant drugs - Zuclopenthixol enhances the sedative response to alcohol and the effects of barbiturates and other CNS depressants.

Hypnotics - As with phenothiazines, Clopixol should not be used concomitantly with large doses of hypnotics due to the possibility of potentiation.

Antihypertensives - Zuclopenthixol should not be given concomitantly with guanethidine or similar acting compounds since neuroleptics such as zuclopenthixol may block their antihypertensive effects.

Levodopa, adrenergic drugs - Zuclopenthixol may reduce the effects of levodopa and adrenergic drugs.

Metoclopramide, piperazine - Concomitant use of metoclopramide or piperazine increases the risk of extrapyramidal disorder.

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

Drugs known to increase the QT interval - 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 the QT interval (e.g. cisapride, lithium) should be avoided.

Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalaemia) 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 Special warnings and precautions for use.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported (see Section 4.8 Adverse Effects). 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.

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 reduced conception rate was noted.

Use in pregnancy
– Pregnancy Category C

The safety of Clopixol in pregnant women has not been established. Clopixol should not be administered to women of child-bearing potential unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the foetus.

Animal studies have shown reproductive toxicity.

In a three-generation study in rats a delay in mating was noted. In an experiment where zuclopenthixol was administered via the diet, impaired mating performance and reduced conception rate was noted.

Zuclopenthixol crosses the placental barrier in small amounts.

Non teratogenic class effect:

Neonates exposed to antipsychotic drugs (including zuclopenthixol) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.

Zuclopenthixol should be used during pregnancy only if the anticipated benefit outweighs the risk and administered dose and duration of treatments should be as low and short as possible.

Use in lactation

Oral administration of the drug to rats during the peri/postnatal period at dose levels of 5 and 15 mg/kg/day resulted in an increase in the number 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 by the dams who were exposed to doses of zuclopenthixol producing maternal toxicity.

Zuclopenthixol passes into breast milk in small amounts; the milk/serum concentration ratio in women is on average 0.3.

Safe use of Clopixol by nursing mothers has not been established, therefore it is recommended that breast-feeding be discontinued in women taking Clopixol.

4.7 Effects on ability to drive and use machines

Zuclopenthixol 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 Adverse effects (Undesirable effects)

Clopixol has been marketed extensively overseas for many years. Adverse events listed below reflect those which have been observed during clinical trials, published reports and in the overseas post marketing period. Events described as "rarely" are those which were reported on 1 - 3 occasions irrespective of the formulation used and without regard to causality, while those described as "occasionally" were reported on 4 - 10 occasions. Other events were reported more frequently (see also the adverse events table below).

Because zuclopenthixol shares many of the pharmacological properties of other thioxanthenes and phenothiazines, the possible occurrence of the known adverse effects of these drug classes exists.

Autonomic Nervous System

Dry mouth, blurred vision, constipation, excessive salivation, excessive perspiration, nausea, difficulty in micturition and urinary retention have been observed.

Miosis, mydriasis, paralytic ileus, polyuria, nasal congestion and glaucoma have been reported with related drugs.

Cardiovascular

Orthostatic dizziness may occur. Tachycardia, palpitations and fainting have been observed.

Hypotension, hypertension, fluctuations in blood pressure, non-specific ECG changes and cardiac arrhythmias have been reported with related drugs.

If hypotension occurs, adrenalin should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result.

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 Special warnings and precautions for use).

Central Nervous System

The most common adverse reaction reported with zuclopenthixol has been extrapyramidal disorder.

Extrapyramidal symptoms, including hypo- and hyperkinetic states, tremor, pseudoparkinsonism, dystonia, hypertonia, rigidity, akathisia, oculogyric crises, opisthotonos, hyper-reflexia and tardive dyskinesia (see below).

Extrapyramidal symptoms may be alarming and patients should be forewarned and reassured (see Section 4.2 Dose and method of administration). Reduction in dosage or, if possible, discontinuation of zuclopenthixol therapy is recommended (see Section 4.4 Special warnings and precautions for use).

Other CNS effects include drowsiness and somnolence.

Metabolic and Endocrine

Weight change and menstrual disturbance have been reported. Transient galactorrhoea has been reported occasionally. Gynaecomastia, thyroid disorder and impotence have been observed rarely.

Related drugs have been associated with breast enlargement, menstrual irregularities, false positive pregnancy tests, peripheral oedema, hypo- and hyperglycaemia and glycosuria.

Persistent Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients during long-term use or may occur after drug therapy has been discontinued. Elderly patients on high dose therapy, especially elderly females, may be at greater risk. The symptoms may be persistent and, in some patients, appear to be irreversible.

The syndrome is characterised by rhythmical, involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. If these symptoms appear, it is suggested that all antipsychotic agents be discontinued. Should it be necessary to reinstitute treatment, increase dosage or change the antipsychotic agent, the syndrome may be masked.

If manifestations are recognised, particularly in patients over the age of fifty, the risk of this syndrome developing may be reduced by avoiding unnecessary neuroleptic medication, reducing the dose or discontinuing the drug altogether (if possible).

It has been reported that if the medication is stopped at the first signs of fine vermicular movements of the tongue, which may be an early manifestation, the syndrome may not develop.

Toxic and Allergic

Alterations in liver function, particularly increased bilirubin levels have been observed. Transient increases in ALT and ALP values may occur. Transient, benign leukopenia has been reported rarely. Peripheral oedema has occasionally been reported. Skin reactions such as pruritus, rash and erythema have been reported rarely.

Eosinophilia, jaundice and increased levels of alkaline phosphatase have been reported with related drugs. Other antipsychotic drugs have been associated with leukopenia, agranulocytosis, thrombocytopenic or non-thrombocytopenic purpura, haemolytic anaemia and pancytopenia.

Discontinuation

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.

Miscellaneous

Lens opacity has been reported rarely.

Other Post-Marketing Events

Post-marketing events from literature and spontaneous reporting for which frequencies have been further defined are provided in the table below. 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).

Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis
Cardiac disorders	Common	Tachycardia, palpitations
	Rare	Electrocardiogram QT prolonged
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Hyperacusis, tinnitus
Endocrine disorders	Rare	Hyperprolactinaemia
Eye disorders	Common	Accommodation disorder, vision abnormal
	Uncommon	Oculogyration, mydriasis
Gastrointestinal disorders	Very common	Dry mouth
	Common	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea
	Uncommon	Abdominal pain, nausea, flatulence
General disorders and administration site conditions	Common	Asthenia, fatigue, malaise, pain
	Uncommon	Thirst, injection site reaction, hypothermia, pyrexia.
Hepato-biliary disorders	Uncommon	Liver function test abnormal
	Very rare	Cholestatic hepatitis, jaundice
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction
Metabolism and nutrition disorders	Common	Increased appetite, weight increased
	Uncommon	Decreased appetite, weight decreased
	Rare	Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia
Musculoskeletal and connective tissue disorder	Common	Myalgia
	Uncommon	Muscle rigidity, trismus, torticollis
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
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state
	Very rare	Neuroleptic malignant syndrome
Renal and urinary disorders	Common	Micturition disorder, urinary retention, polyuria
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism
Respiratory, thoracic and medistianal disorders	Common	Nasal congestion, dyspnoea
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis, pruritus
	Uncommon	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura
Vascular disorders	Uncommon	Hypotension, hot flush
	Very rare	Venous thromboembolism

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

In general, the main therapy for all overdoses is supportive and symptomatic care.

Symptoms

Overdosage may cause somnolence, coma, cramps, convulsions, extrapyramidal symptoms, shock, decreased blood pressure and hyperthermia/hypothermia.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when zuclopenthixol has been taken or 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. No further doses of zuclopenthixol should be administered. Measures to support the respiratory and cardiovascular systems should be instituted. If severe hypotension occurs, an i.v. vasopressor drug should be administered

immediately. Epinephrine (adrenaline) should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal symptoms with an antiparkinsonian medication.

For information on the management of overdose, contact the Poison Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Zuclopenthixol is a potent neuroleptic of the thioxanthene series. The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking activity. The thioxanthenes have high affinity for both the adenylate cyclase-coupled dopamine D1 receptors and for the dopamine D2 receptors; in the phenothiazine group the affinity for D1 receptors is much lower than for D2 receptors, whereas butyrophenones, diphenylbutylpiperidines and benzamides only have affinity for D2 receptors.

In the traditional tests for antipsychotic effect e.g. antagonism of stereotypic behaviour induced by dopamine agonists, the mentioned chemical groups of neuroleptics exhibit equal but dose-dependent activity. However, the antistereotypic effect of butyrophenones, diphenylbutylpiperidines and benzamides is strongly counteracted by the anticholinergic drug, scopolamine, that of the phenothiazines less so, while the antistereotypic effect of the thioxanthenes, e.g. zuclopenthixol, is not, or only very slightly, influenced by concomitant treatment with anticholinergics. Like most other neuroleptics, zuclopenthixol increases the serum prolactin level.

Clinical trials

A clear relationship between serum levels and clinical effects of zuclopenthixol has not been established. However, data from open trials of zuclopenthixol in the treatment of mania and acute paranoid psychosis indicate that the minimum effective serum levels are 5 nanogram/mL (12.5 nmol/L) in acute mania patients of moderate severity; 3 - 4 nanogram/mL (7.5 - 10 nmol/L) in moderately psychotic patients (BPRS 26 - 30 points); and 6 - 8 nanogram/mL (15 - 20 nmol/L) in severely psychotic patients (BPRS 31 - 38 points). Clopixol tablets, when given within the dosage recommendation, provide adequate zuclopenthixol serum levels for effective control of psychoses.

5.2 Pharmacokinetic properties

Absorption

Clopixol tablets

The absolute bioavailability after oral administration of Clopixol 10 mg tablets is 49%. Maximum serum concentrations are reached after approximately 4 hours (2 - 12 hours). The

mean steady state serum level corresponding to 20 mg/day zuclopenthixol (as the dihydrochloride) p.o. is about 13 ng/mL (33 nmol/L). The biological half-life is approximately 20 hours.

Concomitant intake of food enhances the bioavailability by approximately 20% of Clopixol tablets without influencing its absorption rate. C_{max}, t_{max} and elimination half-life (t½) are not altered. The postulated mechanism for this effect is that food reduces the presystemic clearance of zuclopenthixol. This effect is of doubtful clinical relevance and it does not appear that Clopixol tablets need to be given with regard to meals.

Clopixol Acuphase injection

The acetate ester is rather slowly released from the oil and is rapidly hydrolysed to the active substance, zuclopenthixol, upon reaching the body water.

Maximum serum concentrations of zuclopenthixol are reached, on average, 24 to 36 hours after i.m. injection, followed by a gradual decline. Average maximum serum concentration of zuclopenthixol corresponding to a 100 mg i.m. dose of zuclopenthixol acetate is 41 ng/mL (102 nmol/L). 3 days following injection, serum levels are approximately one-third of the maximum.

Clopixol Depot injection

The decanoate ester is slowly released from the oil depot and is rapidly hydrolysed to the active substance, zuclopenthixol, upon reaching the body water phase. Whereas zuclopenthixol itself is relatively short-acting, the decanoate ester in oil provides a predictable, slow-release preparation of the active constituent.

Maximum serum concentrations of zuclopenthixol are reached 3 to 7 days following i.m. injection. The serum concentration curve declines exponentially with a half-life of 19 days, reflecting the rate of release from the depot. The average steady state pre-injection serum level of zuclopenthixol corresponding to a 200 mg dose of zuclopenthixol decanoate every 2 weeks is approximately 10 ng/mL (25 nmol/L).

As no first pass metabolism occurs when a drug is administered parenterally, zuclopenthixol decanoate can be administered in lower doses than oral zuclopenthixol.

A dose of 200 mg/2 weeks or 400 mg/4 weeks zuclopenthixol decanoate is expected to be equivalent to a daily dose of 25 mg zuclopenthixol (as the dihydrochloride).

Distribution

As for other neuroleptics, zuclopenthixol is distributed with highest concentrations of drug and metabolites in liver, lungs, intestines and kidneys and lower concentrations in heart, spleen, brain and blood. The apparent volume of distribution is 20 L/kg and protein binding is approximately 98% at concentrations above the therapeutic range.

Metabolism
The metabolism of zuclopenthixol is mainly by means of sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity.

Excretion
Excretion is mainly via the faecal route and to a smaller degree (about 10%) via the urine. Only about 0.1% of the dose is excreted unchanged in the urine, so the drug load on the kidneys is negligible. The systemic clearance is approximately 0.9 L/min.

Linearity
The kinetics appear to be linear, since highly significant correlations exist between dose and serum level, and between dose and area under the serum concentration curve, respectively.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity
Chronic administration of zuclopenthixol (30 mg/kg/day for 2 years) in rats resulted in small, but significant, increases in the incidence of thyroid parafollicular carcinomas and, in females, of mammary adenocarcinomas and of pancreatic islet cell adenomas and carcinomas. An increase in the incidence of mammary adenocarcinomas is a common finding for D2 antagonists which increase prolactin secretion when administered to rats. An increase in the incidence of pancreatic islet cell tumours has been observed for some other D2 antagonists. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Clopixol tablets

They contain the following excipients: potato starch, lactose monohydrate, microcrystalline cellulose, copovidone, glycerol, purified talc, hydrogenated castor oil and magnesium stearate, with a coating of hypromellose and macrogol 6000, coloured with titanium dioxide and iron oxide red.

Clopixol Acuphase injection

It contains the following excipient: fractionated coconut oil.

Clopixol Depot injection

It contains the following excipient: fractionated coconut oil.

6.2 Incompatibilities

Clopixol Acuphase and Clopixol Depot should not be mixed with depot preparations formulated with a sesame oil vehicle since this will produce changes in pharmacokinetic properties.

Zuclopenthixol acetate should only be mixed with zuclopenthixol decanoate which is also dissolved in coconut oil, and vice versa.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Clopixol tablets
Store below 25°C. Protect from light.

Clopixol Acuphase injections and Clopixol Depot injection
Store below 25°C. Protect from light. Do not remove from carton except immediately prior to use.

6.5 Nature and contents of container

Clopixol tablets
HDPE bottles with a PP child resistant closures of 100 tablets.

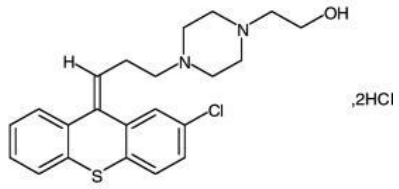
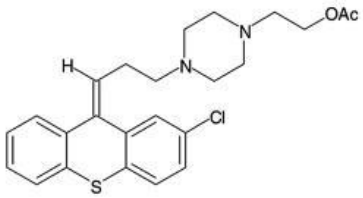
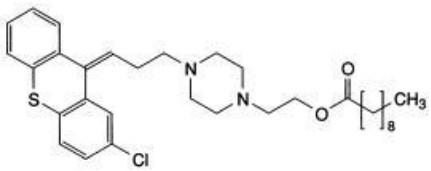
Clopixol Acuphase injection
1 and 2 mL glass ampoules in packs of 5 ampoules.

Clopixol Depot injection
1 mL glass ampoules in packs of 5 ampoules.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Clopixol® Tablets	Clopixol® Acuphase Injection	Clopixol® Depot Injection
Chemical name:		
(Z)-2-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]piperazin-1-ylethanol dihydrochloride	(Z)-2-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]piperazin-1-ylethyl acetate	2-[4-[3-[(Z)-2-chloro-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethyl decanoate
Physical properties:		
Clopixol tablets contain zuclopenthixol hydrochloride, an off-white, granular powder. It is very soluble in water, sparingly soluble in ethanol (96%), slightly soluble in chloroform and very slightly soluble in ether.	Clopixol Acuphase contains the acetate ester of zuclopenthixol. Zuclopenthixol acetate is a yellowish, viscous oil. It is very slightly soluble in water, very soluble in ethanol (96%), ether and dichloromethane.	Clopixol Depot contains the decanoate ester of zuclopenthixol. Zuclopenthixol decanoate is a yellow viscous oily liquid. It is very slightly soluble in water, very soluble in alcohol and methylene chloride.
Molecular formula: Molecular weight		
$C_{22}H_{25}ClN_2OS,2HCl$: 473.9	$C_{24}H_{27}ClN_2O_2S$: 443.0	$C_{32}H_{43}ClN_2O_2S$: 555.3
Structural formula:		
		

CAS number

Clopixol® Tablets	Clopixol® Acuphase Injection	Clopixol® Depot Injection
633-59-0	85721-05-7	64053-00-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Australian Sponsor:

Lundbeck Australia Pty Ltd
1 Innovation Rd
North Ryde NSW 2113
Ph: +61 2 8669 1000

New Zealand Sponsor:
Healthcare Logistics
PO Box 62027
Mt Wellington, Auckland
Ph: +64 9 9185100

9 DATE OF FIRST APPROVAL

20 September 1993

10 DATE OF REVISION

14 March 2025

Summary table of changes

Section Changed	Summary of new information
4.4 and 4.8	Information on extrapyramidal symptoms moved from Section 4.8 to Section 4.4. Addition of warning regarding dysphagia to Section 4.4.

"Clopixol" is the registered trademark of H. Lundbeck A/S.