
Name of Medicine

Clopixol[®]

Zuclopenthixol hydrochloride Film-coated Tablets 10 mg

Clopixol[®] Acuphase

Zuclopenthixol acetate Injection 50 mg/mL

Clopixol[®] Depot

Zuclopenthixol decanoate Injection 200 mg/mL

Presentation

Clopixol tablets

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

Clopixol Acuphase injection

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 Acuphase injection presents as a clear, yellowish oil.

Clopixol Depot injection

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.

Clopixol Depot injection presents as a clear, yellowish oil.

Uses

Actions

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.

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.

Pharmacokinetics

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 ($t_{1/2}$) 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.

Biotransformation

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.

Elimination

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.

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.

Mental retardation associated with psychomotor hyperactivity, agitation, violence and other behavioural disturbances.

Senile dementia with significant paranoid ideas, confusion, disorientation or behavioural disturbances.

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.

Dosage and 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 ($t_{1/2}$) 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.

Agitation in mentally retarded patients

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

Agitation and confusion in senile patients

2 - 6 mg/day orally (preferably given late in the day). If necessary, increase to 10 - 20 mg/day.

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 **Warnings and Precautions**).

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 **Warnings and Precautions**).

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 **Dosage and 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.

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 **Further Information**).

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.

Leucopenia and/or previous agranulocytosis.

Warnings and 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.

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.

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.

Reduced hepatic function - 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 **Dosage and Administration**).

Reduced renal function - 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.

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

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

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

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.

Laboratory tests required - Blood dyscrasias and liver damage have been reported with this class of drugs. 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.

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 **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.

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.

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

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

Safety Experience in Elderly Patients with Dementia-related Psychosis

Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Pregnancy and Lactation

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.

Non teratogenic class effect:

Zuclopenthixol crosses the placental barrier in small amounts.

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.

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

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.

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

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.

Other

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.

Adverse Effects

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

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.

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.

Central Nervous System

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

These symptoms (if they occur) usually appear within the first few days of treatment and can usually be controlled or totally curtailed by reduction in dosage and/or standard antiparkinsonian medication. However, the routine prophylactic use of antiparkinsonian medication is not recommended. Extrapyramidal reactions may be alarming and patients should be forewarned and reassured (see **Dosage and Administration**). Other CNS effects include drowsiness and somnolence.

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.

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 **Warnings and Precautions**).

Vascular Disorders

Incidence of venous thromboembolism - very rare.

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.

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.

Pregnancy, puerperium and perinatal conditions

Neonatal drug withdrawal syndrome – frequency not known.

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 leucopenia 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 leucopenia, 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.

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 **Warnings and Precautions**).

Overdosage

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 further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

Pharmaceutical Precautions

Instructions for Use/Handling

Nil

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.

Shelf Life

2 years

Special Precautions for Storage

Store below 25°C. Protect from light.

Medicine Classification

Prescription only medicine

Package Quantities

Clopixol tablets

- Film-coated tablets containing 10 mg zuclopenthixol as the dihydrochloride.
- Bottles of 100 tablets.

Clopixol Acuphase injection

- Solution for injection containing zuclopenthixol acetate 50 mg/mL, equivalent to zuclopenthixol 45.25 mg/mL.
- 1 and 2 mL glass ampoules in packs of 5 ampoules.

Clopixol Depot injection

- Solution for injection containing zuclopenthixol decanoate 200 mg/mL, equivalent to zuclopenthixol 144.4 mg/mL.
- 1 mL glass ampoules in packs of 5 ampoules.

Further Information

Clopixol® Tablets 10 mg	Clopixol® Acuphase Injection 50 mg/mL	Clopixol® Depot Injection 200 mg/mL
Zuclopenthixol hydrochloride	Zuclopenthixol acetate	Zuclopenthixol decanoate
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-9H-thioxanthene-9-ylidene]propyl]piperazin-1-yl]ethyl decanoate
CAS number:		
633-59-0	85721-05-7	64053-00-5
Molecular formula: Molecular weight		
C ₂₂ H ₂₅ ClN ₂ OS,2HCl: 473.9	C ₂₄ H ₂₇ ClN ₂ O ₂ S: 443.0	C ₃₂ H ₄₃ ClN ₂ O ₂ S: 555.3
Structural formula:		
Excipients:		
Starch - potato, lactose, cellulose - microcrystalline, PVP/VA copolymer, glycerol, talc - purified, castor oil - hydrogenated and magnesium stearate, with a coating of hypromellose and macrogol 6000, coloured with titanium dioxide and iron oxide red CI77491	Coconut oil – fractionated	Coconut oil – fractionated

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.

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Date of Preparation

19 December 2011

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