

PRODUCT MONOGRAPH

Pr **CLOPIXOL**[®]

Zuclopendixol Tablets Lundbeck Std.
(10 mg and 25 mg zuclopendixol as zuclopendixol hydrochloride)
Lundbeck standard

Pr **CLOPIXOL-ACUPHASE**[®]

50 mg/mL Zuclopendixol Intramuscular Injection
(45.25 mg/mL zuclopendixol as zuclopendixol acetate)
Lundbeck standard

Pr **CLOPIXOL**[®] **DEPOT**

200 mg/mL Zuclopendixol Intramuscular Injection
(144.4 mg/mL zuclopendixol as zuclopendixol decanoate)
Lundbeck standard

Antipsychotic Agent

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Pr **CLOPIXOL**[®]
Zuclopendixol Tablets Lundbeck Std.
(as hydrochloride)

Pr **CLOPIXOL-ACUPHASE**[®]
Zuclopendixol Intramuscular Injection

Pr **CLOPIXOL**[®] **DEPOT**
Zuclopendixol Intramuscular Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
oral	tablet / 10 mg, 25 mg	castor oil (hydrogenated), copovidone, ferric oxide, glycerol, hypromellose, lactose, macrogol 6000, magnesium stearate, microcrystalline cellulose, potato starch, talc, titanium dioxide
intramuscular injection	acuphase / 50 mg/mL	medium-chain triglycerides
	depot / 200 mg/mL	medium-chain triglycerides

INDICATIONS AND CLINICAL USE

Clopixol[®] (Zuclopendixol Tablets Lundbeck Std. (as hydrochloride)), Clopixol-Acuphase[®] (zuclopendixol acetate) and Clopixol[®] Depot (zuclopendixol decanoate) are indicated for:

- the management of the manifestations of schizophrenia.

Clopixol[®] (zuclopendixol hydrochloride) may be used during initial treatment and for maintenance treatment. Clopixol-Acuphase[®] (zuclopendixol acetate) is intended for the initial treatment of acute psychotic episodes or exacerbation of psychosis associated with schizophrenia. Clopixol[®] Depot (zuclopendixol decanoate) is intended for maintenance treatment.

Geriatrics (> 65 years of age): The pharmacokinetics, safety, and efficacy of zuclopendixol in elderly patients with schizophrenia have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population.

Pediatrics (< 18 years): The safety and efficacy of zuclopenthixol in children under the age of 18 years have not been established, therefore its use is not recommended.

CONTRAINDICATIONS

- Acute alcohol, barbiturate or opiate intoxication.
- CNS depression due to any cause, comatose states, suspected or established subcortical brain damage or circulatory collapse.
- Patients with known hypersensitivity to thioxanthenes, zuclopenthixol or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Neuroleptic malignant syndrome (NMS) is a rare, sometimes fatal, neurological disorder that has been reported in association with antipsychotic drugs including zuclopenthixol (see WARNINGS AND PRECAUTIONS, Neurologic and ADVERSE REACTIONS).

Elderly Patients with Dementia

Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in elderly patients with dementia showed a mean 1.6 fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zuclopenthixol is not indicated for the treatment of patients with dementia (see PRECAUTIONS, Use in Elderly, Use in Geriatric Patients with Dementia).

Anticholinergic Effects: Zuclopenthixol may potentiate anticholinergic effects of concurrent medications. See OPHTHALMOLOGIC for more details.

Antiemetic Effects: An antiemetic effect of zuclopenthixol has been observed in animals. Since this effect may also occur in man, zuclopenthixol may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumor or intestinal obstruction.

Cardiovascular

Cardiotoxicity: 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 hypokalemia, hypomagnesemia or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (<50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided.

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 (see DRUG INTERACTIONS.)

Cardiovascular Disease: Caution should be used when using zuclopenthixol in patients with advanced cardiovascular disease or in those at risk of developing conduction abnormalities.

Cerebrovascular accidents: An approximately 3-fold increase risk of cerebrovascular adverse events has been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Zuclopenthixol should be used with caution in patients with risk factors for stroke.

Venous Thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. All possible risk factors for VTE should be identified before and during treatment with Clopixol and preventive measures undertaken.

Elderly Patients with Dementia (See section beneath the Serious Warnings and Precautions box.)

Endocrine and Metabolism

Hyperprolactinemia: Antipsychotic drugs elevate prolactin levels with the effect persisting during chronic administration. Since tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, zuclopenthixol should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering zuclopenthixol treatment in patients with pituitary tumors. Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea, and menorrhagia (see ADVERSE REACTIONS).

Chronic administration of zuclopenthixol (30 mg/kg/day for two 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 tumors 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, but it is accepted as not predicting an oncogenic risk in patients.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Genitourinary: Rare cases of priapism have been reported with antipsychotic use, such as zuclopenthixol. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Neutropenia, leukopenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use, including with zuclopenthixol decanoate. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting zuclopenthixol and then periodically throughout the treatment.

Hepatic/Biliary/Pancreatic/Renal

Impaired Liver Function: The use of zuclopenthixol in patients with impaired liver function has not been studied. As zuclopenthixol is extensively metabolized by the liver and primarily excreted in the bile (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics), caution should be exercised in dose selection for patients with this condition.

Impaired Renal Function: The use of zuclopenthixol in patients with impaired renal function has not been studied. Caution should thus be exercised in dose selection for patients with this condition.

Neurologic

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome (NMS) is characterized by hyperthermia, muscle rigidity, altered consciousness, and signs of autonomic instability including irregular blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional signs may include greatly elevated creatine phosphokinase, myoglobinuria and acute renal failure.

The management of NMS should include immediate discontinuation of all antipsychotic drugs including zuclopenthixol, intensive monitoring of symptoms, and treatment of any associated medical problems. There is no general agreement about specific pharmacological treatment for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the reintroduction of therapy should be carefully considered, since recurrence of NMS has been reported.

Patients with Parkinson's Disease: Zuclopenthixol should be used with caution in patients with Parkinsonism, as it is known that dopamine antagonists such as zuclopenthixol, can cause a deterioration of the disease.

Seizures: Zuclopenthixol should be used with caution in patients with a history of convulsive disorders, as drugs of this class are known to lower seizure threshold

Tardive Dyskinesia: is a potentially irreversible neurological syndrome associated with the use of antipsychotic drugs, including zuclopenthixol (see ADVERSE REACTIONS). It is characterized by stereotypical, repetitive, involuntary movements of the jaw, tongue and in some cases, the extremities. Tardive dyskinesia occurs more frequently in elderly patients. However, patients of any age can be affected. The risk of developing tardive dyskinesia and the chance of it becoming irreversible are believed to increase as the duration of treatment and the cumulative dose of antipsychotic drugs increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. Tardive dyskinesia may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment itself, however, may suppress the signs and symptoms of tardive dyskinesia, thereby masking the underlying process.

In view of these considerations, zuclopenthixol should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of zuclopenthixol should be considered.

Occupational Hazards Sedative Effects: Since sedation is known to occur with zuclopenthixol, patients should be cautioned against performing activities requiring a high degree of mental alertness and physical coordination (such as driving a car or operating machinery) until the effect of the drug is determined.

Ophthalmologic

Anticholinergic Effects: Although its anticholinergic effects are weak, zuclopenthixol use should be avoided in patients who are known to have, or suspected of having narrow angle glaucoma.

Photosensitivity Reactions: Photosensitivity reactions, pigmentary retinopathy and lenticular and corneal deposits have been reported with related drugs. Lens opacity has been reported rarely with zuclopenthixol.

Sexual Function / Reproduction

Adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported in patients. These events may have a negative impact on female and/or male sexual function and fertility.

If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are reversible on discontinuation.

Animal studies have shown reproductive toxicity. Administration of zuclopenthixol to male and female rats was associated with a slight delay in mating. In an experiment where zuclopenthixol was administered via the diet, impaired mating performance and reduced conception rate was noted. (See TOXICOLOGY, Reproductive Toxicity)

Special Populations

Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia: An increased risk of cerebrovascular adverse events has been seen in the dementia population in clinical trials with some atypical antipsychotics. The mechanism for this increased risk is not known. There is insufficient data to know if there is an increased risk of cerebrovascular events associated with zuclopenthixol. An increased risk however cannot be excluded. Zuclopenthixol is not indicated in elderly patients with dementia.

Geriatrics (> 65 years of age): The pharmacokinetics, safety, and efficacy of zuclopenthixol in elderly patients with schizophrenia have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population.

Mortality in Geriatric Patients with Dementia-related Psychosis: In elderly patients with dementia-related psychosis, the efficacy and safety of zuclopenthixol has not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zuclopenthixol is not indicated for the treatment of patients with dementia-related psychosis.

Nursing Women: Zuclopenthixol is excreted in human milk with an average milk/serum concentration ratio of approximately 0.3. The safe use of zuclopenthixol during lactation has not been established.

Pediatrics (< 18 years): The safety and efficacy of zuclopenthixol in children under the age of 18 years have not been established, therefore its use is not recommended.

Pregnant Women: The safe use of zuclopenthixol during pregnancy has not been established. Zuclopenthixol was not teratogenic in either rats or rabbits, however, increases in the number of stillbirths, reduced pup survival and delayed development of pups were seen in rats. The clinical significance of these findings is unclear. It has been shown that zuclopenthixol

crosses the placenta of mice.

Neonates exposed to antipsychotic drugs (including zuclopenthixol) during the third trimester of pregnancy are at a risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been 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 intensive care unit support and prolonged hospitalization.

Zuclopenthixol should not be administered during pregnancy unless the expected benefit to the patient outweighs the potential risk to the fetus.

Vascular disease: Zuclopenthixol should be used with caution in patients with risk factors for stroke or with a history of stroke.

ADVERSE REACTIONS

Patients should be advised of the risk of severe constipation during zuclopenthixol treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events were recorded in controlled and uncontrolled European and Canadian clinical trials in which 1922 patients were treated with either Clopixol tablets (zuclopenthixol hydrochloride), Clopixol-Acuphase (zuclopenthixol acetate) or Clopixol Depot (zuclopenthixol decanoate).

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

The most common adverse events reported were drowsiness, fatigue, dizziness, and extrapyramidal symptoms.

Table 1 - Treatment Emergent Adverse Events Reported with Clopixol at a Frequency of >1% from the Combined European and Canadian Clinical Trial Database

ADVERSE EVENT ^a	NUMBER OF PATIENTS (Percentage of Patients)		
	Clopixol Dosage Form		
	Tablet (n=523)	Acuphase (n=588)	Depot (n=811)
Body as a Whole			
Asthenia/Fatigue	79 (15.1)	46 (7.8) ^b	111 (13.7) ^b
Malaise	12 (2.3)	-	-
Pain	9 (1.7)	-	-
Paleness	6 (1.1)	-	-
Syncope	6 (1.2)	-	5 (0.6)
Psychiatric			
Somnolence/Drowsiness	169 (32.3) ^b	95 (16.2) ^{bc}	159 (19.6) ^b
Anxiety/Nervousness	88 (16.9)	24 (4.1)	70 (8.6)
Insomnia	85 (16.2)	27 (4.6) ^b	84 (10.4) ^b
Agitation	52 (9.9)	7 (1.2) ^b	11 (1.4)
Depression	41 (7.8)	18 (3.1)	59 (7.3)
Concentration impaired	40 (7.6)	15 (2.6)	32 (3.9) ^b
Anorexia	20 (3.8)	-	12 (1.5)
Hallucination	18 (3.4)	-	-
Apathy	17 (3.2)	14 (2.4)	7 (0.9)
Confusion	14 (2.7)	1 (0.2)	3 (0.4)
Amnesia	13 (2.5)	12 (2.0)	13 (1.6)
Dreaming Abnormal	12 (2.3)	12 (2.0)	12 (1.5)
Appetite increased	5 (1.0)	1 (0.2)	18 (2.2)
Neurological			
Hypertonia	98 (18.7)	150 (25.5)	37 (4.6)
Tremor	98 (18.7)	122 (20.7) ^b	68 (8.4)
Hyperkinesia (Akathisia)	71 (13.6) ^b	94 (16.0) ^b	107 (13.2)
Extrapyramidal Disorder	68 (13.0)	3 (0.5)	97 (12.0)
Dizziness	59 (11.3)	121 (20.6)	55 (6.8) ^b
Hypokinesia	39 (7.4) ^b	122 (20.7) ^b	82 (10.1)
Vertigo	27 (5.2)	6 (1.0)	16 (2.0)
Headache	26 (5.0)	8 (1.4)	43 (5.3) ^b
Dystonia	25 (4.8)	83 (14.1)	56 (6.9)
Dyskinesia Tardive	15 (2.9)	1 (0.2)	7 (0.9)
Gait Abnormal	11 (2.1)	-	6 (0.7)
Neurological Disorder NOS	9 (1.7)	-	1 (0.1)
Paraesthesia	6 (1.1)	18 (3.1)	15 (1.8)
Dyskinesia	-	1 (0.2)	10 (1.2)
Gastrointestinal			
Mouth dry	79 (15.1)	148 (25.2)	106 (13.1) ^b
Constipation	41 (7.8)	4 (0.7) ^b	51 (6.3) ^b
Salivation increased	40 (7.6)	58 (9.9)	52 (6.4)
Vomiting	17 (3.2)	6 (1.0)	17 (2.1)
GI Disorder NOS	15 (2.9)	1 (0.2)	10 (1.2)
Nausea	10 (1.9)	4 (0.7)	11 (1.4)
Diarrhea	4 (0.8)	4 (0.7)	9 (1.1)
Dyspepsia	-	-	10 (1.2)

ADVERSE EVENT ^a	NUMBER OF PATIENTS (Percentage of Patients)		
	Clopixol Dosage Form		
	Tablet (n=523)	Acuphase (n=588)	Depot (n=811)
Cardiovascular			
Tachycardia	19 (3.6)	58 (9.9)	21 (2.6)
Postural Hypotension	13 (2.5)	2 (0.2)	-
Arterial Hypotension	9 (1.7)	-	-
Palpitation	7 (1.3)	-	15 (1.8)
Musculoskeletal System			
Myalgia	-	-	10 (1.2)
Skin and Appendages			
Sweating increased	16 (3.0)	7 (1.2)	47 (5.8) ^b
Pruritus	-	1 (0.2)	17 (2.1)
Seborrhoea	8 (1.5)	-	2 (0.2)
Skin Disorder	7 (1.3)	-	-
Metabolic and Nutritional			
Weight increase	20 (3.8)	-	17 (2.1)
Weight decrease	17 (3.2)	-	14 (1.7)
Thirst	5 (1.0)	-	17 (2.1) ^b
Vision			
Accommodation Abnormal	29 (5.5)	65 (11.0)	33 (4.1)
Vision Abnormal	19 (3.6)	-	17 (2.1) ^b
Urinary			
Micturition Disorder	16 (3.0)	3 (0.5)	26 (3.2)
Reproductive			
Libido decreased	17 (3.2)	1 (0.2)	11 (1.4)
Menstrual disorder	5 (2.2)	-	12 (4.3) ^b
Ejaculation failure	1 (0.4)	1 (0.3)	8 (1.8) ^b
Anorgasmia female	1 (0.4)	-	3 (1.1)

- a The incidence of adverse events is not directly comparable across formulations, as distinct clinical trials were conducted for each dosage form. Trial duration varied considerably between formulations (i.e., 2-12 weeks for Tablets; 3-9 days for Acuphase; and 4-52 weeks for Depot).
- b Incidence in Canadian studies at least 10 percentage points higher than the combined European and Canadian incidence.
- c Somnolence was not rated as an adverse event in many European Acuphase trials, as sedation was considered a therapeutic effect. Therefore, the incidence of this event is considered under-represented for the Acuphase formulation.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events reported in clinical trials, occurring at rates of 1% or less, are provided in the summary below for all three formulations together:

Body as a Whole: allergic reaction, application site disorder, arthritis, back pain, chest pain, precordial chest pain, conjunctivitis, faintness, fever, hot flushes, toothache

Cardiovascular: hypotension

Gastrointestinal:	abdominal pain, dysphagia, gastric ulcer, glossitis, meteorism
Hematological:	purpura
Neurological:	acute dyskinesia, ataxia, convulsions, hyperreflexia, hypotonia, migraine, oculogyric crisis, speech disorder
Psychiatric:	drug dependence, excitability, irritability, increased libido, melancholia, paroniria
Reproductive:	erectile dysfunction, galactorrhea, gynecomastia, dry vagina
Respiratory:	dyspnea, nasal congestion, pharyngitis, rhinitis
Skin and Appendages:	dermatitis, photosensitivity reaction, abnormal pigmentation, rash, erythematous rash, psoriasiform rash
Special Senses:	mydriasis, hyperacusis, tinnitus
Urinary:	polyuria, urinary incontinence, urinary infection, urinary retention

Post-Market Adverse Drug Reactions

Adverse events not listed above that have been reported since Clopixol was introduced on the market are provided below.

Blood and Lymphatic System Disorders

Thrombocytopenia, leukopenia, neutropenia, agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting zuclopenthixol and then periodically throughout the treatment.

Cardiac Disorders

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 with zuclopenthixol.

Endocrine Disorders

Hyperprolactinaemia

General Disorders

Hypothermia. Peripheral edema has occasionally been reported.

Hepato-biliary Disorders

Cholestatic hepatitis, jaundice.

Alterations in liver function, particularly increased bilirubin levels have occasionally been reported. Transient increases in ALT and ALP values may also occur.

Immune System Disorders

Anaphylactic reaction

Metabolism and Nutrition Disorders

Hyperglycaemia, impaired glucose tolerance, hyperlipidaemia

Musculoskeletal and Connective Tissue Disorders

Muscle rigidity, trismus, torticollis

Nervous System Disorders

Parkinsonism, Neuroleptic Malignant Syndrome (NMS)

Reproductive System Disorders

Priapism

DRUG INTERACTIONS

Overview

Zuclophenixol enhances the sedative response to alcohol and the effects of barbiturates and other CNS depressants. It should not be administered with high doses of hypnotics due to the possibility of potentiation.

Zuclophenixol should not be given concomitantly with guanethidine or similar acting compounds, since antipsychotic drugs such as zuclophenixol may block the antihypertensive effect of these compounds.

Many antipsychotic and tricyclic antidepressant drugs may mutually inhibit the metabolism of each other.

Concomitant use of metoclopramide increases the risk of extrapyramidal symptoms.

Zuclophenixol may antagonize the effects of levodopa and dopamine agonists.

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 zuclophenixol therapy is recommended. If akathisia persists, a benzodiazepine or propranolol may be useful.

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

Long-acting depot antipsychotics (such as Clopixol Depot) 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.

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)
- Some antipsychotics (e.g. thioridazine)
- Some macrolides (e.g. erythromycin)
- Some quinolone antibiotics (e.g. moxifloxacin)

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

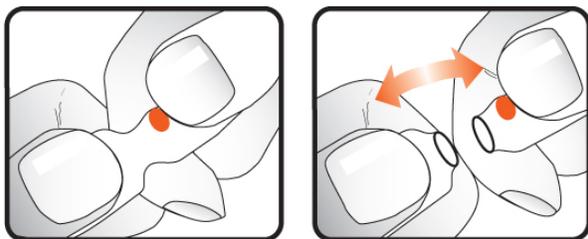
Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalemia) and drugs known to increase the plasma concentration of zuclopenthixol should also be used with caution as they may increase the risk of QT prolongation and malignant arrhythmias.

DOSAGE AND ADMINISTRATION

Administration

Clopixol-Acuphase (zuclopenthixol acetate) and Clopixol Depot (Clopixol Decanoate)

How to open an ampoule:



The ampoule can only be broken in one direction. The breaking point can be found on the neck of the ampoule next to the red dot. The pressure must be applied under the red dot.

Hold the ampoule with the red dot facing up. Position your thumbs on each side of the neck of the ampoule, one on the top of the red dot and the other on the label. Apply pressure using your

index fingers and snap the ampoule in an upward direction. Keep the ampoule away from you at all times when opening.

Dosing Considerations

Clopixol Tablets (zuclopenthixol hydrochloride)

Dosage should be individualized according to the patient's condition. In general, small doses should be used initially and increased until an optimal response is obtained.

Clopixol-Acuphase (zuclopenthixol acetate)

Clopixol-Acuphase is intended for use during acute psychotic episodes or exacerbation of psychosis associated with schizophrenia, when compliance with oral medication may be unreliable. Clopixol-Acuphase has an onset of action within 2-4 hours, and a duration of action of 2-3 days following a single intramuscular injection. Significant dose-dependent sedation occurs within 2 hours of injection, usually reaching a maximum after 8 hours. Tolerance to the sedative effect may develop with repeated injection. Maximum serum concentrations of zuclopenthixol are reached, on average, 24 to 48 hours after injection.

Clopixol-Acuphase is not intended for long-term use, and the duration of treatment should not exceed two weeks. The maximum cumulative dosage should not exceed 400 mg, and the number of injections should not exceed four.

Following treatment with Clopixol-Acuphase, antipsychotic therapy, when indicated, should be continued with either oral or long-acting injectable antipsychotic medications such as Clopixol tablets or Clopixol Depot (zuclopenthixol decanoate), respectively.

Clopixol Acuphase is administered by deep intramuscular injection into the gluteal region. Injection volumes exceeding 2 ml should be distributed between 2 injection sites. Local tolerability is good.

Clopixol Depot (Clopixol Decanoate)

Clopixol Depot is intended for maintenance treatment of chronic schizophrenia in patients who have been stabilized with oral or other short-acting medication, and who might benefit from transfer to long-acting injectable therapy.

Clopixol Depot is administered by deep intramuscular injection into the gluteal region. Injection volumes exceeding 2 ml should be distributed between 2 injection sites. Local tolerability is good.

Co-injection of Clopixol-Acuphase and Clopixol Depot

For patients with exacerbation of chronic psychoses, Clopixol-Acuphase and Clopixol Depot can be mixed in a syringe and given as one injection (co-injection). Since Clopixol-Acuphase and Clopixol Depot are dissolved in the same vehicle, mixing will not affect the pharmacokinetics of either formulation and will allow the administration of an acute and maintenance dose with one injection. **Clopixol-Acuphase cannot be mixed with other antipsychotic depot formulations.**

Subsequent doses of Clopixol Depot and the interval between injections should be adjusted according to the patient's response.

Recommended Dose and Dosage Adjustment

Clopixol Tablets

When initiating treatment with Clopixol tablets, it is recommended that the drug be given in divided doses (BID or TID). During the maintenance phase of treatment Clopixol tablets may be given as a single nighttime dose.

For acute psychosis, the usual starting dose is 10-50 mg/day, which may be increased by 10-20 mg every 2-3 days, according to the patient's response. The usual therapeutic range is 20 mg to 60 mg daily. However, as with other antipsychotic drugs, some patients may require lower, while others may require higher dosage in order to obtain optimal benefit. Daily dosage higher than 100 mg is not recommended. For maintenance therapy, dosage should be reduced to the lowest level compatible with symptom control. The usual maintenance dose is 20-40 mg/day.

Clopixol-Acuphase

Dosage should be individually adjusted according to the patient's condition. The usual dose is 50-150 mg (1-3 mL) administered intramuscularly and repeated if necessary, at intervals of 2-3 days. Some patients may need an additional injection 1 or 2 days after the first injection.

Due to the delay in reaching peak zuclopenthixol blood levels and maximum pharmacologic effect, close supervision is required in order to minimize the risk of over-medication or insufficient suppression of psychotic symptoms.

The maximum cumulative dosage should not exceed 400 mg, and the number of injections should not exceed four.

Tables 2a and 2b below provide guidelines for dosage form conversion. Clopixol tablets should usually be started 2 to 3 days after the last injection of Clopixol-Acuphase. If Clopixol Depot is used for maintenance, it can be given concomitantly with the last injection of Clopixol-Acuphase (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment, Co-injection of Clopixol-Acuphase and Clopixol Depot).

Table 2a - Suggested Dose to be Used When Transferring Patients from Clopixol-Acuphase to Clopixol Tablets

Clopixol-Acuphase Dose	Clopixol Tablet Dose*
50 mg	20 mg daily
100 mg	40 mg daily
150 mg	60 mg daily

* initial total daily dose usually given in divided dosages (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment, Clopixol Tablets).

Table 2b - Suggested Dose to be Used When Transferring Patients from Clopixol-Acuphase to Clopixol Depot

Clopixol-Acuphase Dose	Clopixol Depot Dose*
50 mg	100 mg Q2 weekly
100 mg	200 mg Q2 weekly
150 mg	300 mg Q2 weekly

* See DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment, Clopixol Depot

Clopixol Depot

Close supervision is required during the period following initiation of Clopixol Depot treatment, in order to minimize the risk of over-medication or insufficient suppression of psychotic symptoms. Supplemental oral antipsychotic medication may be required in diminishing dosage during this period.

The usual maintenance dose is 150-300 mg intramuscularly, every 2-4 weeks. Some patients may require higher or lower doses, or shorter intervals between doses.

During treatment with Clopixol Depot, the patient should be maintained at the lowest dose level compatible with adequate symptom control.

Table 3 below provides guidelines for conversion from Clopixol tablets to Clopixol Depot.

Table 3 - Suggested Dose to be Used When Transferring Patients from Clopixol Tablets to Clopixol Depot

Clopixol Tablet Dose	Clopixol Depot Dose*
up to 20 mg daily	100 mg Q2 weekly
25 mg to 40 mg daily	200 mg Q2 weekly
50 mg to 75 mg daily	300 mg Q2 weekly
more than 75 mg daily	400 mg Q2 weekly

* See DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment, Clopixol Depot

Dose Adjustment with Co-injection of Clopixol-Acuphase and Clopixol Depot

See DOSAGE AND ADMINISTRATION, Dosing Considerations, Co-injection of Clopixol-Acuphase and Clopixol Depot.

Use in the Elderly: The use of zuclopenthixol in elderly patients with schizophrenia has not been systematically evaluated. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population.

Impaired Liver Function: The use of zuclopenthixol in patients with impaired liver function has not been studied. As zuclopenthixol is extensively metabolized by the liver and primarily excreted in the bile (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics), caution should be exercised in dose selection for patients with this condition.

Impaired Renal Function: The use of zuclopenthixol in patients with impaired renal function has not been studied. Caution should be exercised in dose selection for patients with this condition.

Missed Dose

Clopixol Tablets

A missed dose should be taken at the next scheduled dose. Doses should not be doubled.

Discontinued Dose

Clopixol Tablets

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.

OVERDOSAGE

The symptoms are likely to be somnolence, coma, extrapyramidal symptoms, convulsions, hypotension, QT prolongation, Torsade de Pointes, cardiac arrest, ventricular arrhythmias, shock, or hyper- or hypothermia.

There is no specific antidote for zuclopenthixol. Treatment should be symptomatic and supportive. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal should be considered. Measures aimed at supporting the respiratory and cardiovascular systems should be instituted. Hypotension and circulatory collapse may be counteracted by use of IV fluids. **Adrenaline (epinephrine) must not be used as a further lowering of blood pressure may result.** In cases of severe extrapyramidal reactions, antiparkinsonian medication should be administered. Close monitoring and medical supervision should continue until the patient recovers.

In managing overdose, the physician should consider the possibility of multiple drug involvement.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Zuclopenthixol, a thioxanthene derivative, has high affinity for both dopamine D₁ receptors and dopamine D₂ receptors. Zuclopenthixol also has high affinity for α_1 -adrenergic and 5-HT₂ receptors. It has weaker histamine H₁ receptor blocking activity, and even lower affinity for muscarinic cholinergic and α_2 -adrenergic receptors.

Pharmacokinetics

The pharmacokinetics of zuclopenthixol appear to be linear over the dosage range studied. A strong correlation exists between dose and steady state serum level, and between dose and area under the serum concentration time curve. The apparent volume of distribution is 20 L/kg. Protein binding is approximately 98%.

Clopixol-Acuphase (zuclopenthixol acetate) and Clopixol Depot (zuclopenthixol decanoate)

Clopixol-Acuphase and Depot are long-acting forms of zuclopenthixol that have been made more lipophilic by esterification with acetic and decanoic acid, respectively. Both esters of zuclopenthixol are dissolved in medium-chain triglycerides and when injected intramuscularly, diffuse slowly from the oil depot to the body water phase where they are rapidly hydrolyzed to the active substance, zuclopenthixol. Once hydrolyzed, zuclopenthixol is distributed, metabolized, and excreted as described.

Absorption:

Clopixol Tablets (zuclopenthixol hydrochloride)

Maximum serum concentrations of zuclopenthixol are reached in approximately 4 hours (range 2-12 hours) following administration. The elimination half-life is approximately 20 hours (range 12-28 hours). The mean steady state serum level of zuclopenthixol corresponding to a daily 20 mg dose of zuclopenthixol hydrochloride is about 13 ng/mL (33 nmol/L).

Clopixol-Acuphase

Maximum serum concentrations of zuclopenthixol are reached, on average, 24 to 48 hours after intramuscular injection, followed by a gradual decline. Average maximum serum concentration of zuclopenthixol corresponding to a 100 mg intramuscular dose of zuclopenthixol acetate is 41 ng/mL (102 nmol/L). Three days after injection, serum levels are approximately one-third the maximum.

Clopixol Depot

Maximum serum concentrations of zuclopenthixol are reached 3 to 7 days following intramuscular injection. The serum concentration time curve declines exponentially with a half-life of 19 days, reflecting the rate of release from the oil depot. Zuclopenthixol decanoate, when given at a dose of 200 mg every 2 weeks, results, on average, in a steady state zuclopenthixol serum concentration of approximately 10 ng/mL (25 nmol/L), when measured immediately prior to the next injection.

Metabolism: The metabolism of zuclopenthixol is mainly by sulfoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of pharmacological activity.

Excretion: Zuclopenthixol is excreted mainly in feces with about 10% excreted in the urine. Approximately 0.1% of a dose is excreted unchanged in the urine. The systemic clearance is approximately 0.9 L/min.

Based on the above characteristics for elimination it is reasonable to assume that reduced kidney function is likely not to have much influence on the serum levels of parent drug.

STORAGE AND STABILITY

Clopixol tablets (zuclopenthixol hydrochloride) should be stored between 15°C and 25°C.

Clopixol-Acuphase (zuclopenthixol acetate) is provided in single-dose ampoules which should be stored between 15°C and 25°C, and protected from light. Discard unused portion.

Clopixol Depot (zuclopenthixol decanoate) is provided in single-dose ampoules which should be stored between 15°C and 25°C, and protected from light. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Clopixol Tablets (zuclopenthixol hydrochloride):

Clopixol 10 mg tablets: Each light red-brown, round, biconvex, film-coated tablet contains 10 mg zuclopenthixol as zuclopenthixol hydrochloride. Supplied in bottles of 100 tablets.

Clopixol 25 mg tablets: Each red-brown, round, biconvex, film-coated tablet contains 25 mg zuclopenthixol as zuclopenthixol hydrochloride. Supplied in bottles of 100 tablets.

In addition to the active ingredient, zuclopenthixol hydrochloride, each tablet also contains the following non-medicinal ingredients: castor oil (hydrogenated), copovidone, ferric oxide, glycerol, hypromellose, lactose, macrogol 6000, magnesium stearate, microcrystalline cellulose, potato starch, talc, titanium dioxide.

Clopixol-Acuphase (zuclopenthixol acetate):

Supplied in colourless glass ampoules of 1 mL and 2 mL, in packages of 5 ampoules.

Each 1 mL and 2 mL ampoule of Clopixol-Acuphase contains zuclopenthixol acetate 50 mg/mL (equivalent to zuclopenthixol 45.25 mg/mL) in medium-chain triglycerides.

Clopixol Depot (zuclopenthixol decanoate):

Supplied in clear vials of 10 mL and in clear glass ampoules of 1 mL in packages of 10 ampoules.

Each 1 mL ampoule and each 10 mL vial of Clopixol Depot contains zuclopenthixol decanoate 200 mg/mL (equivalent to 144.4 mg/mL zuclopenthixol) in medium-chain triglycerides.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Clopixol[®] (Zuclopenthixol Tablets Lundbeck Std. (as hydrochloride))

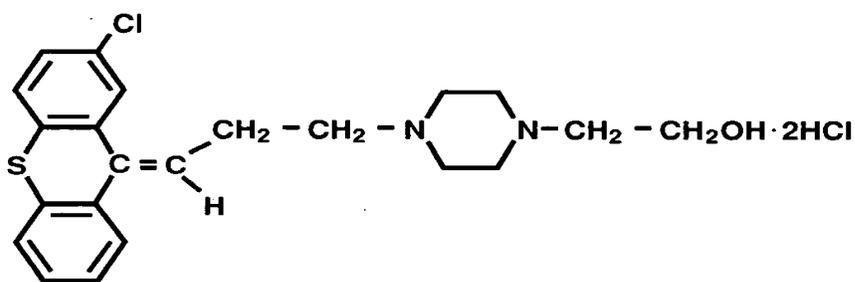
Drug Substance

Proper name: Zuclopenthixol Tablets Lundbeck Std.

Chemical name: cis(Z)-4-[3-(2-chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol dihydrochloride

Molecular formula and molecular mass: $C_{22}H_{25}ClN_2OS \cdot 2HCl$
473.91

Structural formula:



Physicochemical properties: Zuclopenthixol hydrochloride is an off-white, granular powder having a slight odor and a bitter taste. Melting range about 250°C. It is very soluble in water, sparingly soluble in 96% ethanol, slightly soluble in chloroform and very slightly soluble in ether.

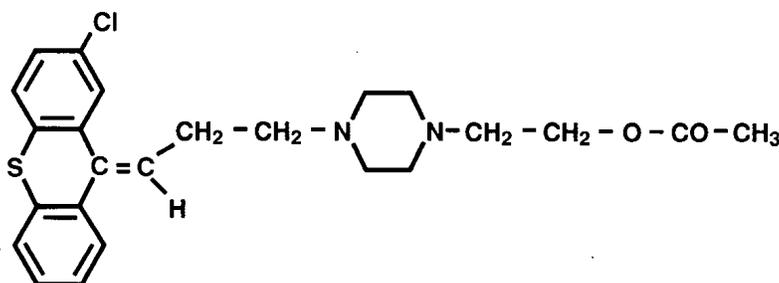
Clopixol-Acuphase (zuclopenthixol acetate)
Drug Substance

Proper Name: Zuclopenthixol acetate

Chemical Name: cis(Z)-4-[3-(2-chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol acetate

Molecular formula and molecular mass: $C_{24}H_{27}ClN_2O_2S$
443.04

Structural Formula:



Physical Form: Zuclopenthixol acetate is a yellowish viscous oil with a slight odor. It can crystallize with a melting point of about 50°C. It is very slightly soluble in water, but very soluble in 96% ethanol, ether, and dichloromethane.

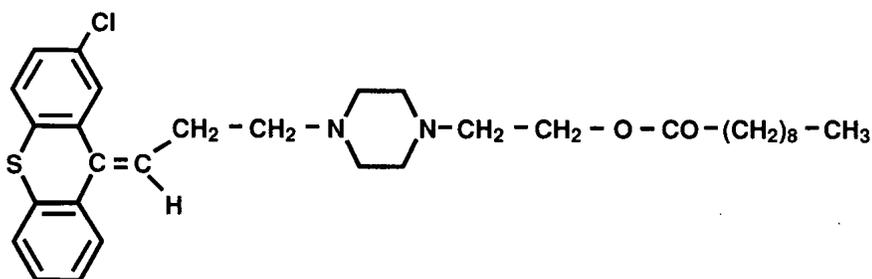
Clopixol Depot (zuclopenthixol decanoate)
Drug Substance

Proper Name: Zuclopenthixol decanoate

Chemical Name: cis(Z)-4-[3-(2-chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol decanoate

Molecular formula and molecular mass: $C_{32}H_{43}ClN_2O_2S$
555.27

Structural Formula:



Physical Form: Zuclopenthixol decanoate is a yellowish viscous oil with a slight odor. It can crystallize with a melting point of about 30°C. It is very slightly soluble in water, but very soluble in 96% ethanol, ether, and chloroform.

DETAILED PHARMACOLOGY

Zuclopenthixol has proven to be a potent neuroleptic in all the behavioural studies for neuroleptic (dopamine receptor blocking) activity, i.e. antagonism of stereotypic behaviour in rodents induced by dopamine agonists (methylphenidate, amphetamine, apomorphine), antiemetic and antistereotypic effect in dogs, antagonism of hyperactivity in rodents induced by 6,7-ADTN, antagonism of circling behaviour induced by DA agonists in unilaterally 6-OHDA lesioned rats, catalepsy and inhibition of conditioned avoidance response. The acute pharmacological effect of zuclopenthixol resembles that of perphenazine and haloperidol in many respects. Correlation is found between the potency of individual neuroleptics in the in vivo test models, the affinity for dopamine D₂ binding sites in vitro and the average, daily oral antipsychotic doses.

Like most neuroleptics, zuclopenthixol possess α ₁-adrenolytic properties. The peripheral α ₁-adrenoceptor blockade is claimed to be responsible for cardiovascular side effects such as orthostatic hypotension and tachycardia. Zuclopenthixol is approximately half as potent as chlorprothixene. The antihistaminic potency is of the same order of magnitude as that of diphenhydramine and, therefore, zuclopenthixol possibly may diminish the alcohol-disulfiram reaction. The anticholinergic activity is very weak. Inhibition of locomotor activity, inhibition of electrically-induced EEG arousal reaction and prolongation of alcohol- and barbiturate-induced sleeping time indicate a sedative action of zuclopenthixol. Like most other neuroleptics, zuclopenthixol increases the serum prolactin level.

TOXICOLOGY

Acute Toxicity

Zuclopenthixol hydrochloride: Zuclopenthixol has a low acute toxicity with LD₅₀ values in mice of 539-653 mg/kg after oral administration and 85-91 mg/kg after intravenous administration. Values in rats of 320-386 mg/kg after oral administration and greater than 800 mg/kg after intramuscular administration were found. The animals became markedly sedated and convulsive attacks were seen before death. Histological examination revealed no abnormalities.

Zuclopenthixol acetate: LD₅₀ was greater than 402 mg/kg after intramuscular injection to mice and rats. Clinical signs and mortality were also recorded for 7 days after dosing. Marked sedation was seen one hour after dosing and lasted for several days. During this period the animals did not eat or drink; they died from starvation and dehydration. Histological examination revealed no abnormalities.

Zuclopenthixol decanoate: The LD₅₀ was greater than 1600 mg/kg after intramuscular injection to mice and rats. Clinical signs and mortality were also recorded for 7 days after dosing. Sedation occurred only 24 hours after dosing. The animals were able to eat and drink and therefore, the mortality rates with decanoate were less during the 7 days, in spite of the considerably higher doses as compared to zuclopenthixol acetate. Histological examination revealed no abnormalities.

Chronic Toxicity

Zuclopenthixol hydrochloride: In chronic toxicity studies carried out for 6 months in rats and dogs only the highest orally administered doses (30 mg/kg/day) of zuclopenthixol caused weak unspecific toxic reactions. No significant histopathological, biochemical or hematological changes were noted; therefore, there were no findings of concern for the therapeutic use of zuclopenthixol.

In rats, inhibition of body weight gain was the only treatment-related finding. In dogs, the high dosages caused loss of condition because of sedation, slight hypotrophy of the organs of the genital tract (decreased weight of ovaries, uterus, testicles and prostate), very mild increase of lipofuscin granules in liver cells and posterior lenticular opacities. However, since no report on lenticular opacities in patients has appeared during the many years the isomeric mixture of clopenthixol has been used in Europe in contrast to some phenothiazines; this finding is considered to be without clinical relevance.

Zuclopenthixol acetate: Four-week toxicity studies with zuclopenthixol acetate in oil have been performed in rats and dogs. The rats received 5, 15 or 30 mg/kg every third day and the dogs 5 or 25 mg/kg every third day. The investigations did not demonstrate any serious changes that could be ascribed to zuclopenthixol acetate.

Zuclopenthixol decanoate: Six-month toxicity studies with zuclopenthixol decanoate in oil have been performed in rats and dogs. The rats received 10, 35 or 120 mg/kg every week and the dogs 10, 30 or 100 mg/kg every week. The investigations did not demonstrate any serious changes that could be ascribed to zuclopenthixol decanoate. A dose-dependent, slight sedation was seen, but this effect gradually receded during continued medication.

Reproduction and Teratology

Zuclopenthixol hydrochloride: Zuclopenthixol hydrochloride was administered to pregnant rats at dose levels of 0, 1, 5, 15, and 30 mg/kg/day p.o. on the 6th to the 15th day of gestation. No major effects were found and based on data from reproduction toxicity studies there is no reason to have special concern for the use of zuclopenthixol in women of childbearing potential. Skeletal examination revealed only slight retardation of skull ossification in the control group and in the 1 and 30 mg/kg/day groups. However, zuclopenthixol was not considered to be responsible. In the 15 to 30 mg/kg/day dose groups the mean body weight gain of the pregnant rats was reduced from day 15 and 9 of the gestation period, respectively. The clinical significance of these findings is unclear and it is possible that the effect on pups was due to neglect from the dams that were exposed to doses of zuclopenthixol producing maternal toxicity.

Zuclopenthixol hydrochloride was also administered to rabbits at dose levels of 2, 8, and 30 mg/kg/day p.o. and at dose levels of 0, 3, 9.5 and 30 mg/kg/day p.o. over day 6 to 18 of gestation to determine any embryotoxicity or teratogenicity. The animals were killed on day 29 of gestation and the fetuses examined. In the embryotoxicity study no dose-related effects were demonstrated on the implantations and in the teratogenicity study no dose-related clinical signs were noted; abortions occurred in all groups but the incidence was not excessive or dose-related.

In a fertility study, male rats were dosed for 10 weeks prior to mating and the female rats were dosed for 3 weeks prior to mating, during pregnancy, and until weaning. The dose levels administered were 0, 1, 5, and 15 mg/kg/day orally by gavage. The length of the mating period was increased in the 5 and 15 mg/kg/day dose groups, the mating period being almost twice as long as that of the control group. However, no dose-dependent teratological changes were seen in any of the fetuses apart from a significant increase in the frequency of wavy ribs in the 15 mg/kg/day group. The litter size and the litter weight were not affected by the treatment, except in the highest dosage group, 15 mg/kg/day. The progeny development was considered normal and no adverse effects were observed in the third generation.

Zuclopenthixol acetate: No reproduction studies have been performed on zuclopenthixol acetate, as it is hydrolyzed to zuclopenthixol and acetic acid and therefore reference is made to the study on zuclopenthixol hydrochloride.

Zuclopenthixol decanoate: Zuclopenthixol decanoate dissolved in vegetable oil as the vehicle was administered subcutaneously to four groups of 20 mated mice on day 6 of gestation. The groups received the vehicle, 10, 20 or 50 mg/kg of zuclopenthixol decanoate, respectively.

The maternal body weight was recorded on day 0, from day 6 to 15 and on day 18 of gestation. All mice were killed on day 18 of pregnancy. The uterus from each animal was excised, weighed and examined for total number of implantations, number of fetal resorptions (early and late) and number of live and dead fetuses. The weight of each litter was measured.

No indications of adverse effect on pregnancy or fetal development were observed in any of the groups. In conclusion, zuclopenthixol decanoate is without selective embryotoxicity or specific teratogenicity in the mouse.

The effect of zuclopenthixol decanoate was also studied in the rat. In spite of a body weight loss from commencement of treatment to day 9 and a statistically significant depression of maternal body weight in the 50 mg/kg group including day 15 of gestation, no indications of adverse effects on pregnancy and fetal development were observed. Consequently zuclopenthixol decanoate in vegetable oil is devoid of selective embryotoxicity or specific teratogenicity in the rat.

Zuclopenthixol decanoate dissolved in vegetable oil has been given intramuscularly to three groups of 22 mated rabbits. The dose levels were 10, 20, and 50 mg/kg of zuclopenthixol decanoate. A control group of 22 mated rabbits received 0.25 mL/kg i.m. of vegetable oil.

Maternal body weight was recorded on day 0 and from day 6-29 of pregnancy. All rabbits were killed on day 29 of gestation. The uterus and ovaries were removed and the number and distribution of all live fetuses, early deaths and late deaths were noted. The number of corpora lutea graviditatis was counted. The viscera were examined and fetuses were stained with alizarin for skeletal examination.

Neither the maternal body weight gains nor the weights of the fetuses were reduced by the treatments. No effects of the soft tissues or skeleton and ossification were detected in the fetuses following visceral dissection and staining of the skeletons. Consequently zuclopenthixol decanoate in vegetable oil is devoid of teratogenic potential in the rabbit.

Mutagenicity

Zuclopenthixol hydrochloride has been tested for mutagenicity in the Ames test with 5 different strains of *Salmonella typhimurium* bacteria with and without rat liver microsome fraction. The highest concentration tested showed an antibacterial effect but no mutagenic effects were seen with any of the concentrations or strains tested.

Additional studies (human lymphocytes and mouse micronucleus test) with zuclopenthixol hydrochloride also gave negative results. Since the results of these tests were negative and the molecular structure of zuclopenthixol is not related to any other molecule with known mutagenic potential it is concluded that zuclopenthixol has no mutagenic potential.

Carcinogenicity

Male and female rats (250 of each) of the Wistar strain were divided to five groups of 50 males and 50 females. The animals received zuclopenthixol hydrochloride at dosages of 2, 10, or 30

mg/kg/day in the diet for 2 years. Two control groups received untreated diet. No effect on tumor incidence or the number of benign/malignant tumor-bearing animals was seen following the administration of zuclopenthixol hydrochloride. There was also no significant organ-related toxicity amongst the various non-tumor microscopic findings.

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PART III: CONSUMER INFORMATION

^{Pr}Clopixol[®]

Zuclopendixol Tablets Lundbeck Std.
(10 mg and 25 mg zuclopendixol as zuclopendixol hydrochloride)

^{Pr}Clopixol-Acuphase[®]

50 mg/mL Zuclopendixol Intramuscular Injection
(45.25 mg/mL zuclopendixol as zuclopendixol acetate)

^{Pr}Clopixol[®] Depot

200 mg/mL Zuclopendixol Intramuscular Injection
(144.4 mg/mL zuclopendixol as zuclopendixol decanoate)

This leaflet is part III of a three-part "Product Monograph" published when ^{Pr}Clopixol[®], ^{Pr}Clopixol-Acuphase[®] and ^{Pr}Clopixol[®] Depot were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Clopixol. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information leaflet carefully before you start your medicine, even if you have taken this drug before. Keep this leaflet handy in order to consult while taking your medication.

Clopixol has been prescribed only for you. Do not give it to anybody else.

ABOUT THIS MEDICATION

What the medication is used for:

Clopixol is a prescription medicine that belongs to a family of medicines used to treat schizophrenia.

You may be given Clopixol in the form of tablets or by injection. Depending on the circumstances, your doctor will decide which form of Clopixol is right for you.

Clopixol tablets need to be taken **every day** to be effective.

If you receive Clopixol by injection, it will be administered by a doctor or nurse. There are actually two forms of Clopixol injection, one which is effective when administered every 2-3 days, and another which is effective when administered as infrequently as once every 2-4 weeks.

What it does:

Clopixol belongs to a group of medicines known as antipsychotics (also called neuroleptics). These medicines act on nerve pathways in specific areas of the brain and help to correct certain chemical imbalances that are causing the symptoms of your illness.

When it should not be used:

- If you are allergic to any of its ingredients (see WHAT THE

NON-MEDICINAL INGREDIENTS ARE)

- If you suffer from impaired consciousness due to the influence of alcohol or drugs such as barbiturates and opiates, or as a result of brain damage, shock (circulatory collapse), or being in a comatose state
- If you suffer from depression

What the medicinal ingredient is:

Each Clopixol[®] contains Zuclopendixol Tablets Lundbeck Std. (as hydrochloride). Clopixol-Acuphase injection contains zuclopendixol acetate. Clopixol Depot injection contains zuclopendixol decanoate.

What the non-medicinal ingredients are:

Clopixol tablets:

castor oil (hydrogenated), copovidone, ferric oxide, glycerol, hypromellose, lactose, Macrogol 6000, magnesium stearate, microcrystalline cellulose, copovidone, potato starch, talc, titanium dioxide

Clopixol-Acuphase:

medium-chain triglycerides (vegetable oil)

Clopixol-Depot:

medium-chain triglycerides (vegetable oil)

What dosage forms it comes in:

Clopixol is available as a tablet and as an injection.

Tablets: ^{Pr}Clopixol[®] tablets are available in two strengths. The 10 mg tablet is light-red brown and the 25 mg tablet is red-brown.

Injection: There are two forms of Clopixol for intramuscular injection. ^{Pr}Clopixol-Acuphase[®] is a 50 mg/mL solution (45.25 mg/mL zuclopendixol as zuclopendixol acetate) and ^{Pr}Clopixol[®] Depot is a 200 mg/mL solution (144.4 mg/mL zuclopendixol as zuclopendixol decanoate).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Neuroleptic malignant syndrome (NMS) is a rare, but life-threatening, disorder of the nervous system that has been linked with drugs such as Clopixol. It is characterized by high fever, unusual stiffness of the muscles and disorder of your consciousness, sweating and fast heart rate.

BEFORE you use Clopixol talk to your doctor or pharmacist if:

- you have used Clopixol or any other treatment for schizophrenia before and if you had any problems
- you are taking any other prescription or non-prescription medicines
- you are pregnant or thinking of becoming pregnant, or if you are breast-feeding
- you regularly drink a lot of alcohol

- you have any liver problems, Parkinson's disease or have ever had seizures
- you have dementia
- you have glaucoma
- you have any kidney problems
- you have risk factors for stroke (e.g. smoking, high blood pressure).
- you have hypokalemia or hypomagnesia (too little potassium or magnesium in your blood)
- you have a history of cardiovascular disorders
- you or someone in your family has a history of blood clots
- you are being treated for cancer (applies to Clopixol Depot only)
- you use any other antipsychotic medicine
- you are allergic to any of its ingredients (see ABOUT THIS MEDICATION, What The Medicinal Ingredient Is, What the Non-medicinal Ingredients Are)

It is important that you tell your doctor about all your past and present medical conditions.

Effects on Newborns:

In some cases, babies born to a mother taking Clopixol during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

Effects on Fertility:

Animal studies have shown that Clopixol affects fertility. Please ask your doctor for advice.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Clopixol include:

- tricyclic antidepressant medicines
- guanethidine and similar medicines (used to lower the blood pressure)
- barbiturates and similar medicines
- levodopa and similar medicines (used to treat Parkinson's disease)
- metoclopramide (used in the treatment of gastro-intestinal disorders)
- other antipsychotic medicines (e.g. thioridazine)
- medicines that change the heartbeat (e.g. quinidine, amiodarone, sotalol, erythromycin, moxifloxacin, lithium)

Clopixol may increase the sedative effects of alcohol making you drowsier. It is recommended not to drink alcohol during treatment with Clopixol.

Consult your doctor before taking other medications, including over-the-counter medicines and herbal remedies. Some drugs can

produce additional side-effects when they are used in combination with Clopixol.

PROPER USE OF THIS MEDICATION

Usual dose:

Clopixol Tablets: It is very important that you take Clopixol exactly as your doctor instructs you. Never increase or decrease the amount of Clopixol you are taking unless your doctor tells you to. Clopixol may be taken with or without food.

Discontinued dose:

Abrupt discontinuation of Clopixol Tablets may be accompanied by withdrawal symptoms. The most common symptoms are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation. You may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and decrease within 7 to 14 days.

Clopixol Injection: If you are prescribed Clopixol by intramuscular injection, it will be given by a doctor or nurse. It is very important to keep your scheduled appointments for the injections.

Overdose:

Contact your doctor or nearest hospital emergency department as soon as you realize you have taken too much Clopixol, even if you do not feel sick. Symptoms of overdose may include:

- somnolence
- coma
- unusual movements
- convulsions
- shock
- high or low body temperature

Changes in the heartbeat including irregular heartbeat or slow heart rate has been seen when Clopixol has been given in overdose together with medicines known to affect the heart.

Missed dose:

Clopixol Tablets: If you miss a dose, take it as soon as you remember, as long as it is more than 6 hours before the next dose is due. If it is less than 6 hours before the next dose is due, just take your next regularly scheduled dose and try not to miss any more. Do not try to make up for a missed dose by doubling up on the next dose.

Clopixol Injection: If you miss an appointment, contact your doctor as soon as possible in order to schedule a new appointment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

At the beginning of treatment, Clopixol may make you feel drowsy and dizzy so you should not drive a car or use any tools or

machines until you are sure Clopixol does not affect your mental alertness.

Side-effects that have been reported by patients taking Clopixol include: muscle spasm, stiffness, shaking or uncontrolled body movements. These can happen in different parts of the body, such as the tongue, face, mouth, jaw, eyes, hands, arms and legs.

Contact your doctor if this happens to you.

Other possible side-effects include dry mouth, dizziness, blurred or altered vision (difficulty reading small print), constipation, excessive salivation or sweating, trouble passing urine. Decreases in blood pressure, increases in heart rate, weight changes, skin rash, decreased sexual interest or function, and changes in your monthly cycle (if you are female).

In addition, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.

Your doctor should check your body weight before starting Clopixol and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting Clopixol. They will monitor blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Tell your doctor or pharmacist if you think you have any of these or other effects while taking Clopixol.

Any fever (increased temperature) or soreness of the mouth, gums, or throat that happens while you are taking Clopixol should be reported to your doctor **immediately**.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
		Only if severe	In all cases	
Common	Racing heart (tachycardia), a sensation of a rapid, forceful, or irregular beating of the heart (palpitations)		✓	
	Tremor, twisting or repetitive movements or abnormal postures due to sustained muscle contractions (dystonia), increased muscle stiffness (hypertonia)	✓		
Uncommon	Unusual movements of the mouth and tongue		✓	
	Yellowing of the skin and the white in the eyes and extremities.		✓	
	High fever, unusual stiffness of the muscles and disorder of your consciousness, especially if occurring with sweating and fast heart rate			✓
	Circular movement of the eye (oculogyration)		✓	
	Convulsion			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
		Only if severe	In all cases	
Uncommon	Rash, skin reaction due to sensitivity to light (photosensitivity reaction)		✓	
	Bleeding underneath the skin seen by red or purple discolorations on the skin (purpura)		✓	
	Severe allergic reaction (symptoms include skin rash, hives, swelling, difficulty breathing)			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
	New or worsening constipation		✓	

This is not a complete list of side effects. For any unexpected effects while taking Clopixol, contact your doctor or pharmacist.

HOW TO STORE IT

Clopixol Tablets should be kept in a safe place, between 15°C and 25°C.

Clopixol-Acuphase and Clopixol Depot are single-use vials that should be kept in a safe place, between 15°C and 25°C, protected from light.

Keep Clopixol out of the reach of children.

Safely discard any Clopixol that has passed the expiry date on the label.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to:

Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions or concerns and to find the full product monograph prepared for healthcare professionals, go to <http://www.lundbeck.ca> or contact the sponsor, Lundbeck Canada Inc. at 1-800-586-2325.

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