**Product Monograph**

**Including Patient Medication Information**

**Pr CLOPIXOL®**

zuclopenthixol tablets

For oral use

10 mg and 25 mg of zuclopenthixol (as zuclopenthixol hydrochloride)

**Pr CLOPIXOL ACUPHASE®**

zuclopenthixol acetate injection

Solution

For intramuscular use

50 mg/mL of zuclopenthixol acetate

**Pr CLOPIXOL® DEPOT**

zuclopenthixol decanoate injection

Solution

For intramuscular use

200 mg/mL of zuclopenthixol decanoate

Lundbeck standard

Antipsychotic Agent

Lundbeck Canada Inc.
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H4S 0A9

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## Part 1: Healthcare Professional Information

### 1. Indications

CLOPIXOL (zuclopenthixol hydrochloride), CLOPIXOL ACUPHASE (zuclopenthixol acetate injection) and CLOPIXOL DEPOT (zuclopenthixol decanoate injection) are indicated for:

- the management of the manifestations of schizophrenia.

CLOPIXOL (zuclopenthixol tablets as zuclopenthixol hydrochloride) may be used during initial treatment and for maintenance treatment. CLOPIXOL ACUPHASE (zuclopenthixol acetate injection) is intended for the initial treatment of acute psychotic episodes or exacerbation of psychosis associated with schizophrenia. CLOPIXOL DEPOT (zuclopenthixol decanoate injection) is intended for maintenance treatment.

### 1.1. Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT in pediatric patients under the age of 18 years have not been established, therefore Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

### 1.2. Geriatrics

**Geriatrics (> 65 years of age):** The pharmacokinetics, safety, and efficacy of CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT in geriatric patients with schizophrenia have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for a geriatric patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

### 2. Contraindications

CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are contraindicated in:

- Acute alcohol, barbiturate or opiate intoxication.
- Central Nervous System (CNS) depression due to any cause, comatose states, suspected or established subcortical brain damage or circulatory collapse.
- Patients who are hypersensitive to this drug, thioxanthenes, or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

### 3. Serious Warnings and Precautions Box

- Neuroleptic malignant syndrome (NMS) is a rare, sometimes fatal, neurological disorder that has been reported in association with antipsychotic drugs including zuclopenthixol (see 7 Warnings and Precautions, Neurologic and 8.5 Post-Market Adverse Reactions).
- **Increased mortality in geriatric patients with dementia:** Geriatric patients with dementia treated with antipsychotic drugs are at an increased risk of death compared to those treated with placebo (see 7.1.4 Geriatrics). CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are not approved for use in geriatric patients with dementia.

## 4. Dosage and Administration

### 4.1. Dosing Considerations

Patients on long-term therapy (CLOPIXOL or CLOPIXOL DEPOT), particularly on high doses, should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

**CLOPIXOL**

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**

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 (see 4.4 Administration).

**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 DEPOT**

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 (see 4.4 Administration).

**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) (see 4.4 Administration).

**CLOPIXOL ACUPHASE cannot be mixed with other antipsychotic depot formulations.**

### 4.2. Recommended Dose and Dosage Adjustment

**CLOPIXOL**

When initiating treatment with CLOPIXOL (tablets), it is recommended that the drug be given in two or three divided doses (i.e., BID or TID). During the maintenance phase of treatment CLOPIXOL 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 1a and 1b below provide guidelines for dosage form conversion. CLOPIXOL 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 4.1 Dosing Considerations, Co-injection of CLOPIXOL ACUPHASE and 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 2 below provides guidelines for conversion from CLOPIXOL to CLOPIXOL DEPOT.

**Table 1a Suggested Dose to be Used When Transferring Patients from CLOPIXOL ACUPHASE to CLOPIXOL**

| CLOPIXOL ACUPHASE Dose | CLOPIXOL 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 4.2 Recommended Dose and Dose Adjustment, CLOPIXOL).

**Table 1b 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 4.2 Recommended Dose and Dose Adjustment, CLOPIXOL DEPOT.

**Table 2 Suggested Dose to be Used When Transferring Patients from CLOPIXOL to CLOPIXOL DEPOT**

| CLOPIXOL 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 4.2 Recommended Dose and Dose Adjustment, CLOPIXOL DEPOT.

**Dose Adjustment with Co-injection of CLOPIXOL ACUPHASE and CLOPIXOL DEPOT**

See 4.1 Dosing Considerations, Co-injection of CLOPIXOL ACUPHASE and CLOPIXOL DEPOT.

**Special Populations**

**Use in pediatric patients:** Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

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

**Use in patients with hepatic impairment:** 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 10.3 Pharmacokinetics), caution should be exercised in dose selection for patients with this condition.

**Use in patients with renal impairment:** 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.

### 4.2.1. Discontinuing Treatment

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.

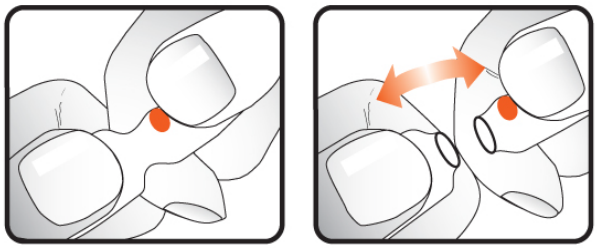
## 4.4. Administration

CLOPIXOL

Tablets shall be swallowed with water and not chewed.

CLOPIXOL ACUPHASE and CLOPIXOL DEPOT

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.

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 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

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

**CLOPIXOL ACUPHASE cannot be mixed with other antipsychotic depot formulations.**

## 4.5. Missed Dose

**CLOPIXOL (tablets)**

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

**CLOPIXOL ACUPHASE and CLOPIXOL DEPOT**

In case of a missed dose, it shall be administered as soon as possible. The following dose would then be administered as per the usual dosing interval.

## 5. Overdose

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. 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 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6. Dosage Forms, Strengths, Composition, and Packaging

**Table 3 - Dosage Forms, Strengths, and Composition**

| Route of Administration | Dosage Form / Strength/Composition | Non-Medicinal Ingredients |
|---|---|---|
| oral | tablet 10 mg, 25 mg zuclopenthixol (as zuclopenthixol hydrochloride) | castor oil (hydrogenated), copovidone, ferric oxide, glycerol, hypromellose, lactose, macrogol 6000, magnesium stearate, microcrystalline cellulose, potato starch, talc, titanium dioxide |
| intramuscular injection | solution 50 mg/mL (as zuclopenthixol acetate) | medium-chain triglycerides |
| | solution 200 mg/mL (as zuclopenthixol decanoate) | medium-chain triglycerides |

**Description**

**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.

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

**CLOPIXOL ACUPHASE**:

Clear, yellowish oil, practically free from particles, 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 in medium-chain triglycerides.

**CLOPIXOL DEPOT**:

Clear, yellowish oil, practically free from particles, supplied in clear glass ampoules of 1 mL in packages of 10 ampoules.

Each 1 mL ampoule of CLOPIXOL DEPOT contains zuclopenthixol decanoate 200 mg/mL in medium-chain triglycerides.

## 7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

### General

#### *Anticholinergic Effects*

Zuclopenthixol may potentiate anticholinergic effects of concurrent medications. See 7 Warnings and Precautions, 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

Caution should be used when using zuclopenthixol in patients with advanced cardiovascular disease or in those at risk of developing conduction abnormalities. Zuclopenthixol should be used with caution in patients with risk factors for stroke or with a history of stroke.

***QT interval:*** As with other drugs belonging to the therapeutic class of antipsychotics, zuclopenthixol may cause QT prolongation (see 8.5 Post-Market Adverse Reactions). Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, zuclopenthixol should be used with caution in susceptible individuals (with hypokalemia, hypomagnesia 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 9.4 Drug-Drug Interactions).

***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.

## Dependence, Tolerance and/or Abuse Liability

Zuclopenthixol has not been systematically studied in humans or animals for its potential for abuse, tolerance, or physical dependence. Withdrawal symptoms have been described after abrupt discontinuation of zuclopenthixol therapy (see 4.2.1 Discontinuing Treatment).

## Driving and Operating Machinery

***Occupational Hazards Sedative Effects:*** Sedation is known to occur with zuclopenthixol. While taking CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination if they are experiencing any of these effects.

## 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 8.5 Post-Market 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 $D_2$ 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 $D_2$ 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 (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

***Lactose***

Because CLOPIXOL tablets contain lactose monohydrate, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take CLOPIXOL tablets.

## 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

Thrombocytopenia, 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 (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

***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, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT and preventive measures undertaken.

### Hepatic/Biliary/Pancreatic

***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 10.3 Pharmacokinetics), caution should be exercised in dose selection for patients with this condition.

### Monitoring and Laboratory Tests

Patients should have baseline and periodic monitoring of blood glucose and body weight.

Complete blood count (CBC) should be tested prior to starting zuclopenthixol and then **periodically** throughout the treatment.

### 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:*** Tardive dyskinesia is a potentially irreversible neurological syndrome associated with the use of antipsychotic drugs, including zuclopenthixol (see 8.2 Clinical Trial 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 geriatric 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.

***Extrapyramidal reactions:*** Extrapyramidal reactions may occur, especially during the first few days after an injection and in the early days of treatment. Similarly, these may occur with the tablets especially in the early days of treatment. In most cases these side effects can be satisfactorily controlled by reduction of dosage and/or use of antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesia and may aggravate them. Reduction in dosage or, if possible, discontinuation of zuclopenthixol therapy is recommended. In persistent akathisia, a benzodiazepine or propranolol may be useful.

*Dysphagia*: Dysphagia can occur secondary to Extrapyramidal symptoms as well to sialorrhea, sedation and Neuroleptic malignant syndrome and may lead to life-threatening complications such as aspiration pneumonia and choking. CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT should be used with caution in patients at risk for aspiration pneumonia (see 7.1.4 Geriatrics and 8.3 Less Common Clinical Trial Adverse Reactions).

## 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.

## Renal

***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.

## Reproductive Health

- **Fertility**

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 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

- **Function**

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

## 7.1. Special Populations

### 7.1.1. Pregnancy

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 (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

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.

### 7.1.2. Breastfeeding

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.

### 7.1.3. Pediatrics

**Pediatrics (< 18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of zuclopenthixol in pediatric patients under the age of 18 years have not been established; therefore Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

### 7.1.4. Geriatrics

**Geriatrics (> 65 years of age):** The pharmacokinetics, safety, and efficacy of zuclopenthixol in geriatric patients with schizophrenia have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for a geriatric patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions in this population (see 4.2 Recommended Dose and Dosage Adjustment).

### Use in Geriatric Patients with Dementia

***Overall Mortality:*** In a meta-analysis of 13 controlled clinical trials, geriatric patients with dementia treated with atypical antipsychotic drugs had an increased risk of mortality compared to placebo.

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. CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are not indicated for the treatment of geriatric patients with dementia.

***Cerebrovascular Adverse Events (CVAEs) Including Stroke in Geriatric 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 geriatric patients with dementia.

## 8. Adverse Reactions

### 8.1. Adverse Reaction Overview

The most frequently reported adverse reactions include somnolence, extrapyramidal disorder and dry mouth, which are categorized as very common (frequency >10%). Insomnia, tremor, dizziness, fatigue, headache, palpitations, constipation, and salivary hypersecretion are reported as common (frequency ≥1% and <10%).

The most severe reactions reported are convulsions as uncommon (frequency ≥0.1% and <1%), QT prolongation as rare (frequency ≥0.01% and <0.1%) and NMS as very rare (frequency <0.01%).

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.

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.

### 8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adverse events were recorded in controlled and uncontrolled European and Canadian clinical trials in which 1922 patients were treated with either CLOPIXOL (zuclopenthixol hydrochloride), CLOPIXOL ACUPHASE (zuclopenthixol acetate) or CLOPIXOL DEPOT (zuclopenthixol decanoate).

**Table 4 Treatment Emergent Adverse Events Reported with CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT at a Frequency of >1% from the Combined European and Canadian Clinical Trial Database**

| System organ class/preferred term | CLOPIXOL (n=523) (%) | CLOPIXOL ACUPHASE (n=588) (%) | CLOPIXOL DEPOT (n=811) (%) |
|---|---|---|---|
| **Body as a Whole** | | | |
| Asthenia/Fatigue | 79 (15.1) | 46 (7.8)[b] | 111 (13.7)[b] |

| System organ class/preferred term | CLOPIXOL (n=523) (%) | CLOPIXOL ACUPHASE (n=588) (%) | CLOPIXOL DEPOT (n=811) (%) |
|---|---|---|---|
| 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] |

| System organ class/preferred term | CLOPIXOL (n=523) (%) | CLOPIXOL ACUPHASE (n=588) (%) | CLOPIXOL DEPOT (n=811) (%) |
|---|---|---|---|
| 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) |
| **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) | - | - |

| System organ class/preferred term | CLOPIXOL (n=523) (%) | CLOPIXOL ACUPHASE (n=588) (%) | CLOPIXOL DEPOT (n=811) (%) |
|---|---|---|---|
| **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 CLOPIXOL; 3-9 days for CLOPIXOL ACUPHASE; and 4-52 weeks for CLOPIXOL 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 CLOPIXOL ACUPHASE trials, as sedation was considered a therapeutic effect. Therefore, the incidence of this event is considered under-represented for the CLOPIXOL ACUPHASE formulation.

## 8.3. Less Common Clinical Trial Adverse Reactions

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

**Blood and Lymphatic system disorders:** Purpura

**Cardiac Disorders:** Hypotension

**Ear and Labyrinth Disorders:** Hyperacusis, tinnitus

**Eye Disorders:** Conjunctivitis

**Gastrointestinal Disorders:** Abdominal pain, dysphagia, gastric ulcer, glossitis, meteorism, toothache

**General Disorders and Administration Site conditions:** Application site disorder, chest pain, precordial chest pain, fever, hot flushes

| | |
|---|---|
| **Immune System Disorders:** | Allergic reaction |
| **Musculoskeletal and Connective Tissue Disorders:** | Arthritis, back pain |
| **Nervous System Disorders:** | Acute dyskinesia, ataxia, convulsions, hyperreflexia, hypotonia, migraine, oculogyric crisis, speech disorder, mydriasis, faintness |
| **Psychiatric Disorders:** | Drug dependence, excitability, irritability, increased libido, melancholia, paroniria |
| **Renal and Urinary Disorders:** | Polyuria, urinary incontinence, urinary infection, urinary retention |
| **Reproductive System and Breast Disorders:** | Erectile dysfunction, galactorrhea, gynecomastia, dry vagina |
| **Respiratory, Thoracic and mediastinal disorders:** | Dyspnea, nasal congestion, pharyngitis, rhinitis |
| **Skin and Subcutaneous Tissue Disorders:** | Dermatitis, photosensitivity reaction, abnormal pigmentation, rash, erythematous rash, psoriasiform rash |

## 8.5. Post-Market Adverse Reactions

Adverse events not listed above that have been reported since CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT were introduced on the market are provided below.

### Blood and Lymphatic System Disorders

Thrombocytopenia, leukopenia, neutropenia, agranulocytosis

### 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

### Gastrointestinal disorders

Flatulence

### General Disorders and Administration Site Reactions

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, hypersensitivity

### Metabolism and Nutrition Disorders

Hyperglycaemia, impaired glucose tolerance, hyperlipidaemia, decreased appetite

### Musculoskeletal and Connective Tissue Disorders

Muscle rigidity, trismus, torticollis

### Nervous System Disorders

Parkinsonism, Neuroleptic Malignant Syndrome (NMS)

### Pregnancy, puerperium and perinatal conditions

Drug withdrawal syndrome neonatal

### Reproductive System and Breast Disorders

Priapism

### Vascular Disorders

Venous thromboembolism

## 9. Drug Interactions

### 9.1. Serious Drug Interactions

- CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are contraindicated in barbiturate, opiate or alcohol intoxication (see 9.4 Drug-Drug Interactions).
- QT prolongation may occur due to interaction between CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT and other drugs, including antipsychotics, class Ia and III antiarrhythmics, some macrolides, some quinolone antibiotics, lithium and CYP2D6 inhibitors. Caution is warranted when CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are co-administered with these drugs (see 9.4 Drug-Drug Interactions).

### 9.2. Drug Interactions Overview

Zuclopenthixol 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.

Zuclopenthixol should not be given concomitantly with adrenergic antagonists or similar acting compounds, since antipsychotic drugs such as zuclopenthixol 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.

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

Since zuclopenthixol is partly metabolized 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.

## 9.3. Drug-Behaviour Interactions

The interaction of CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT with individual behavioural risks (e.g., cigarette smoking, cannabis use) has not been studied.

## 9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 5 - Established or Potential Drug-Drug Interactions**

| [Non-proprietary name(s) of the drug product(s)] | Source of evidence | Effect | Clinical comment |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Alcohol | Not known | Enhancement of the sedative effect of alcohol | Alcohol should be avoided |
| Barbiturates and other CNS depressants | Not known | Potentiation of the effects of barbiturates and other CNS depressants | CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT should not be administered along with high doses of hypnotic drugs |
| Adrenergic antagonists and similar acting drugs | Not known | No/reduced antihypertensive effect of these drugs | CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT should not be administered concomitantly |
| Antipsychotics and Tricyclic antidepressant (TCA) | Not known | Inhibition of metabolism of CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT and/or the interacting other antipsychotic/TCA | Caution is warranted |
| Metoclopramide | Not known | Increased risk of extrapyramidal symptoms | Caution is warranted |
| Levodopa and dopamine agonist drugs | Not known | Reduced effect of levodopa and dopamine agonist | Caution is warranted |
| CYP2D6 inhibitors | Not known | - Decreased clearance of zuclopenthixol<br>- Increased risk of QT prolongation and malignant arrythmia | Caution is warranted |

| | | | |
|---|---|---|---|
| Drugs with myelosuppressive effect | Not known | Increased myelosuppression effect | 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. |
| - Class I and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol)<br>- Some antipsychotics (e.g. thioridazine)<br>- Some macrolides (e.g., erythromycin)<br>- Some quinolone antibiotics (e.g., moxifloxacin)<br>- Lithium | Not known | Exacerbation of QT prolongation due to additive effect | Co-administration with CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT should be avoided. |
| Thiazide diuretics | Not known | Increased risk of QT prolongation and malignant arrhythmia due to electrolyte disturbance (hypokalemia) | Caution is warranted with concomitant administration |

### 9.5. Drug-Food Interactions

CLOPIXOL may be taken with or without food.

### 9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10. Clinical Pharmacology

### 10.1. Mechanism of Action

Zuclopenthixol, a thioxanthene derivative, has high affinity for both dopamine $D_1$ receptors and dopamine $D_2$ receptors. Zuclopenthixol also has high affinity for $\alpha_1$-adrenergic and 5-$HT_2$ receptors. It has weaker histamine $H_1$ receptor blocking activity, and even lower affinity for muscarinic cholinergic and $\alpha_2$-adrenergic receptors.

### 10.2. Pharmacodynamics

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 $D_2$ binding sites *in vitro* and the average, daily oral antipsychotic doses.

Like most neuroleptics, zuclopenthixol possess $\alpha$1-adrenolytic properties. The peripheral $\alpha$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.

### 10.3. 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.

CLOPIXOL ACUPHASE and CLOPIXOL DEPOT

CLOPIXOL ACUPHASE and CLOPIXOL 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.

**Table 6 - Summary of CLOPIXOL Pharmacokinetic Parameters**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | Not known | 4 hours | 20 hours | Not known | 0.9 L/min | 20 L/kg |

**Table 7 - Summary of CLOPIXOL DEPOT Pharmacokinetic Parameters**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | Not known | 3-7 days | 19 days | Not known | 0.9 L/min | 20 L/kg |

**Table 8 - Summary of CLOPIXOL ACUPHASE Pharmacokinetic Parameters**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | 41 ng/ml (Dose 100 mg) | 24-48 hours | Not known | Not known | 0.9 L/min | 20 L/kg |

**Absorption**

CLOPIXOL

Maximum serum concentrations of zuclopenthixol are reached in approximately 4 hours (range 2-12 hours) following administration. Oral bioavailability is about 44%. 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.

**Distribution**

The apparent volume of distribution is 20 L/kg. Protein binding is approximately 98%.

**Metabolism**

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

**Elimination**

The elimination half-life is approximately 20 hours (range 12-28 hours). 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.

**Special populations and conditions**

- **Geriatrics**

No specific studies have been performed with zuclopenthixol acetate in geriatric patients. However, studies with zuclopenthixol dihydrochloride and zuclopenthixol decanoate have shown no pharmacokinetic difference in this patient group.

- **Hepatic Insufficiency**

No data available.

- **Renal Insufficiency**

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.

## 11. Storage, Stability, and Disposal

**CLOPIXOL** should be stored between 15°C and 25°C. Any expired material should be disposed of in accordance with local requirements.

**CLOPIXOL ACUPHASE** 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** is provided in single-dose ampoules which should be stored between 15°C and 25°C and protected from light. Discard unused portion.

## Part 2: Scientific Information

## 13. Pharmaceutical Information

**CLOPIXOL**

**Drug Substance**

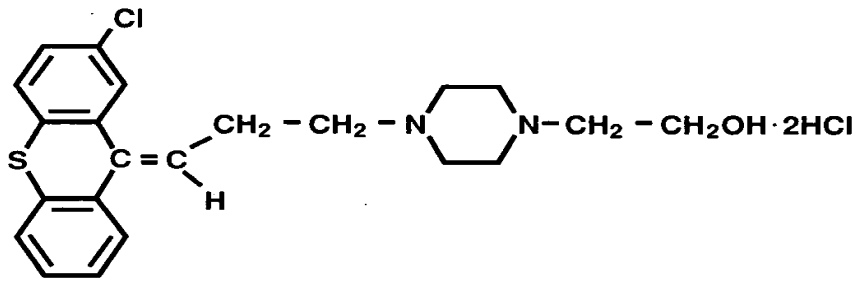
Non-proprietary name of the drug substance(s): zuclopenthixol tablets

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

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

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.

Pharmaceutical standard: Lundbeck standard

**CLOPIXOL ACUPHASE**

**Drug Substance**

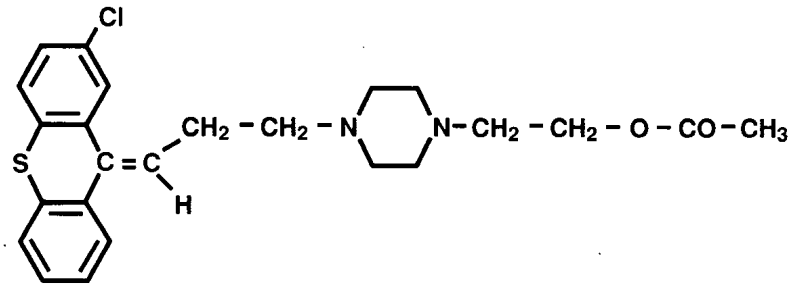
Non-proprietary name of the drug substance(s): Zuclopenthixol acetate injection

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

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

443.04

Structural formula:



Physicochemical properties: 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.

Pharmaceutical standard: Lundbeck standard

**CLOPIXOL DEPOT**

**Drug Substance**

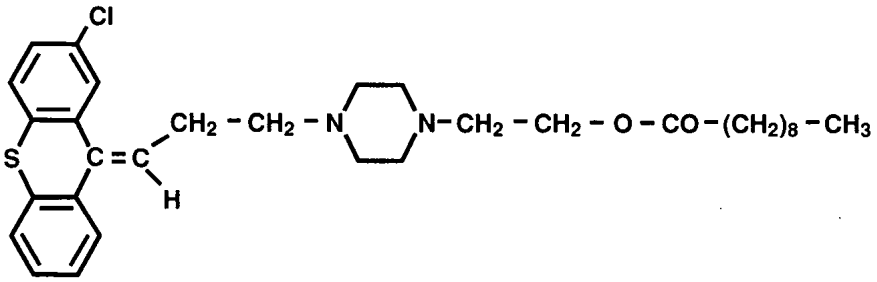
Non-proprietary name of the drug substance(s): Zuclopenthixol decanoate injection

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:



Physicochemical properties: 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.

Pharmaceutical standard: Lundbeck standard

## 14. Clinical Trials

### 14.1. Clinical Trials by Indication

Clinical trial data on which the indication was originally authorized are not available.

## 15. Microbiology

No microbiological information is required for this drug product.

## 16. Non-Clinical Toxicology

**General toxicology:**

**Acute Toxicity**

CLOPIXOL (Zuclopenthixol hydrochloride): Zuclopenthixol has a low acute toxicity with $LD_{50}$ 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.

CLOPIXOL ACUPHASE (Zuclopenthixol acetate): $LD_{50}$ 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.

CLOPIXOL DEPOT (Zuclopenthixol decanoate): The $LD_{50}$ 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**

CLOPIXOL (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.

CLOPIXOL ACUPHASE (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.

CLOPIXOL DEPOT (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.

**Genotoxicity:**

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.

**Reproductive and developmental toxicology:**

CLOPIXOL (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 $6^{th}$ to the $15^{th}$ 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.

CLOPIXOL ACUPHASE (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.

CLOPIXOL DEPOT (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.

## Patient Medication Information

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

Pr **CLOPIXOL** ®

**zuclopenthixol tablets**

Pr **CLOPIXOL ACUPHASE** ®

**zuclopenthixol acetate injection**

Pr **CLOPIXOL** ® **DEPOT**

**zuclopenthixol decanoate injection**

This Patient Medication Information is written for the person who will be taking **CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT**, talk to a healthcare professional.

**Serious warnings and precautions box**

**Risk of death in elderly patients with dementia:**

- CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT belong to a group of medicines called antipsychotics. These medicines have been linked to a higher rate of death when used in elderly patients with dementia (loss of memory and other mental abilities).
- CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are not to be used if you are elderly and have dementia.

**Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but potentially life-threatening condition that has been reported with the use of antipsychotic medications like CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT. Symptoms include:

- severe muscle stiffness or inflexibility with high fever,
- rapid or irregular heartbeat,
- sweating,
- state of confusion or reduced consciousness

**What CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are used for:**

CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are used to treat symptoms of schizophrenia in adults. Not all people with this disorder have the same symptoms. Some of the most common symptoms of schizophrenia may include:

- hallucinations (seeing, feeling, hearing or smelling things that are not there)
- delusions (believing things that are not true)
- paranoia (not trusting others or feeling very suspicious)
- avoiding family members and friends and wanting to be alone

- feeling depressed, anxious or tense

CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are not a cure for your condition, but they can help manage your symptoms and help you feel better.

**How CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT work:**

Antipsychotic medications affect the chemicals that allow your nerve cells to communicate with each other (neurotransmitters). Illnesses that affect the brain may be due to certain chemicals (dopamine and serotonin) in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Exactly how CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT work is unknown. However, they seem to adjust the balance of these chemicals.

**The ingredients in CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are:**

Medicinal ingredients:

- CLOPIXOL: zuclopenthixol (as zuclopenthixol hydrochloride).
- CLOPIXOL ACUPHASE: zuclopenthixol acetate.
- CLOPIXOL DEPOT: zuclopenthixol decanoate.

Non-medicinal ingredients:

- CLOPIXOL: castor oil (hydrogenated), copovidone, ferric oxide, glycerol, hypromellose, lactose, Macrogol 6000, magnesium stearate, microcrystalline cellulose, potato starch, talc, and titanium dioxide
- CLOPIXOL ACUPHASE: medium-chain triglycerides
- CLOPIXOL DEPOT: medium-chain triglycerides

**CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT come in the following dosage forms:**

- CLOPIXOL tablets: 10 mg and 25 mg zuclopenthixol (as zuclopenthixol hydrochloride).
- CLOPIXOL ACUPHASE solution for injection: 50 mg/mL zuclopenthixol acetate.
- CLOPIXOL DEPOT solution for injection: 200 mg/mL zuclopenthixol decanoate.

**Do not use CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT if:**

- you are allergic to:
  - zuclopenthixol or to any of the other ingredients in CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT.
  - thioxanthenes (group of medicines used to treat nervous, mental and emotional conditions).
- you suffer from impaired consciousness (central nervous system depression) due to:
  - the influence of alcohol or drugs such as barbiturates and opioids;
  - brain damage;
  - insufficient blood flow to the tissues of your body as a result of problems with your circulatory system (circulatory collapse);
  - being in a deep state of prolonged unconsciousness (comatose state); or
  - any other causes.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT. Talk about any health conditions or problems you may have, including if you:**

- have had an allergic reaction to any medicine that you have taken to treat your condition.
- are taking any other medicines.
- are pregnant, think you might be pregnant or are planning to become pregnant. CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT can cross the placenta barrier and may harm your unborn baby. Therefore, taking these medicines during pregnancy is not recommended unless you and your healthcare professional decide that the potential benefits markedly outweigh the potentials risks to your baby.
- are breast-feeding or planning to breast-feed. CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT can pass into your breast milk and harm your baby. Talk to your healthcare professional about the best way to feed your baby if you take CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT.
- drink alcohol or use recreational drugs.
- have liver or kidney problems.
- have Parkinson's disease as CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT may worsen your condition.
- have a history of seizures (fits). CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT may increase your risk of seizure by lowering your seizure threshold.
- are elderly and have dementia.
- have narrow angle glaucoma or pressure inside your eye(s).
- have had a stroke or are at risk for stroke.
- have been told by a healthcare professional that you have low levels of potassium or magnesium in your blood.
- have or have a family history of:
  - heart problems
  - any problems with the way your heart beats
  - heart disease
- have risk factors for developing blood clots such as:
  - a family history of blood clots
  - are over the age of 65
  - are smoking
  - are overweight
  - have had a recent major surgery (such as hip or knee replacement)
  - are not able to move due to air travel or other reasons
  - are taking oral birth control ("The Pill")
- have or have had breast cancer.
- have tumours in your pituitary gland.
- have diabetes or a family history of diabetes as CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT may increase your blood sugar levels.
- know that you have or have had a low white blood cell count in the past.
- are at risk for aspiration pneumonia.
- have one of the following rare hereditary diseases:
  - galactose intolerance

- Lapp lactase deficiency
- glucose-galactose malabsorption

CLOPIXOL tablets contain lactose.

**Other warnings you should know about:**

**Tardive dyskinesia (TD):** CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT, like other antipsychotic medications, can cause potentially irreversible muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body.

**Hyperprolactinemia** (increased levels of prolactin): CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT can raise your levels of a hormone called "prolactin". This is measured with a blood test. Symptoms may include:

- In men:
  - swelling in the breast
  - difficulty in getting or maintaining an erection or other sexual dysfunction
- In women:
  - discomfort in the breasts
  - leaking of milk from the breasts (even if not pregnant)
  - missing your menstrual period or other problems with your cycle

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

**Effects in newborns:** In some cases, babies born to mothers taking CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT during pregnancy have symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may get better on their own. Be prepared to get immediate medical help for your baby if they:

- have trouble breathing
- are overly sleepy
- have muscle stiffness or floppy muscles (like a rag doll)
- are shaking
- are having trouble feeding

**Driving and using machines:** CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT can cause drowsiness. Before you do tasks which may require special attention, you should wait until you know how you react to CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT.

**Check-ups and testing:** Your healthcare professional may do check-ups and tests before you start taking CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXAL DEPOT and during your treatment. These may include:

- blood tests to monitor your:
  - blood sugar levels.
  - complete blood cell count. This test measures the number and quality of the red blood cells, white blood cells and platelets.
  - prolactin levels (a hormone in your body).
- body weight checks to monitor any weight gain.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Serious drug interactions:**

Serious drug interactions with CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT include:

- Barbiturates, used to treat insomnia, anxiety and seizures
- Opioids, used to relieve pain
- Alcohol. You should not drink alcohol while taking CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT.
- Certain antipsychotic medications (e.g., thioridazine)
- Medicines used to treat an abnormal heart beat (e.g., quinidine, amiodarone, sotalol)
- Certain antibiotics (e.g., erythromycin, moxifloxacin)
- Lithium, used to treat manic episodes in bipolar disorder
- Medicines called "CYP2D6 inhibitors".

**The following may also interact with CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT:**

- Other antipsychotic medications.
- Hypnotics (also known as "sleeping pills"), used to treat insomnia
- Medicines used to treat high blood pressure (e.g., adrenergic antagonists).
- Medicines used to treat depression (e.g., tricyclic antidepressants).
- Medicines used to treat Parkinson's disease (e.g., levodopa) and similar medicines called "dopamine agonists".
- Medicines that can cause bone marrow suppression (bone marrow unable to produce blood cells) such as therapies/medications used to treat cancer.
- Medicines called "anticholinergics", which causes constipation or may affect your ability to empty your bladder.
- Metoclopramide, used to relieve nausea and treat the symptoms of slow stomach emptying.
- Medicines known to cause an electrolyte imbalance (e.g., thiazide diuretics, also known as "water pills")

**How to take CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT:**

- Take CLOPIXOL tablets or get CLOPIXOL ACUPHASE or CLOPIXOL DEPOT injections exactly as prescribed by your healthcare professional.
- Your healthcare professional will prescribe the lowest effective dose.
- CLOPIXOL tablets may be taken with or without food. Swallow tablets with water. Do **NOT** chew them.
- CLOPIXOL ACUPHASE and CLOPIXOL DEPOT are given by:
  - injection into the muscle (intramuscular) of your buttock.
  - a healthcare professional in a healthcare setting.
- If you stop taking your tablets or coming for your injections, your symptoms may return. **Do not stop your treatment unless told to do so by your healthcare professional.**

- You may feel withdrawal symptoms if you suddenly stop your treatment. These may include: nausea, vomiting, loss of appetite, diarrhea, runny nose, sweating, muscle aches and pain, "pins and needles" sensations, trouble sleeping, or feeling restless, anxious or agitated. You may also experience vertigo, alternate feelings of warmth or coldness, and shaking (tremors). Symptoms may begin within 1 to 4 days of withdrawal and decrease within 7 to 14 days.

**Usual dose:**

The dose of CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT prescribed to you will depend on your condition. Your healthcare professional may change your dose depending on how you respond to your treatment.

**CLOPIXOL** tablets:

- For acute treatment: Usual starting dose: 10 mg to 50 mg per day given in divided doses. Your dose may be increased by 10 mg to 20 mg every 2 to 3 days depending on how you respond to CLOPIXOL. Usual dosage range: 20 mg to 60 mg per day.
- For maintenance treatment: Usual dosage range: 20 to 40 mg per day.
- Maximum daily dose: 100 mg.

**CLOPIXOL ACUPHASE** injection (for acute treatment):

- Usual dosage range: 50 mg to 150 mg. Injection may be repeated every 2 to 3 days if necessary. Some patients may need an additional injection 1 to 2 days after the first injection.
- Maximum cumulative dose: 400 mg.
- Not recommended for treatment longer than 2 weeks.

**CLOPIXOL DEPOT** injection (for maintenance treatment):

- Usual dosage range: 150 mg to 300 mg every 2 to 4 weeks.

**Overdose:**

Symptoms of an overdose with CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT may include:

- drowsiness
- state of deep unconsciousness (coma)
- unusual movements
- convulsions
- low blood pressure
- slow, rapid or irregular heartbeat
- insufficient blood flow to the tissues of your body (circulatory shock)
- heart stops beating suddenly (cardiac arrest)
- high or low body temperature

If you think you, or a person you are caring for, have taken too much CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed dose:**

It is important not to miss your scheduled dose.

- **CLOPIXOL** tablets: If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make up for the missed dose.
- **CLOPIXOL ACUPHASE** and **CLOPIXOL DEPOT** injections: If you miss an appointment, contact your healthcare professional **right away** to let them know you missed your injection. Your healthcare professional will advise you when to come next for your scheduled appointment.

**Possible side effects from using CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT:**

These are not all the possible side effects you may have when taking CLOPIXOL, CLOPIXOL ACUPHASE or CLOPIXOL DEPOT. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT may include:

- Drowsiness, or trouble falling or staying asleep,
- Dizziness, or feeling like you or the room is spinning (vertigo)
- Nausea or vomiting
- Lack of energy
- General feeling of discomfort
- Headache
- Fever
- Hot flashes
- Feeling anxious, agitated or irritable
- Trouble concentrating, or lack of interest or concern
- Abnormal dreams
- Migraine
- Pain at the injection site (for CLOPIXOL ACUPHASE and CLOPIXOL DEPOT)
- Joint pain, or muscle aches or pain
- Back or abdominal pain
- Decreased or increased appetite, changes in body weight
- Dry mouth, increased salivation, indigestion, feeling bloated, diarrhea
- Confusion, memory loss
- Itchy skin, skin rash, skin sensitive to light, skin redness, abnormal pigmentation of the skin, purple coloured spots and patches
- Vision problems, eye inflammation, dilated pupils
- Ringing in the ears, increased sensitivity to sounds
- “pins and needles” sensation on the skin
- Increased sweating
- Shortness of breath
- Sore throat or stuffy nose
- Problems with speech
- Problems with urination
- Abnormal walking pattern
- Feeling faint
- Changes in sex drive, difficulty to achieve orgasm, difficulty to get or keep an erection
- Breast growth in males

**Serious side effects and what to do about them**

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| **Common** | | | |
| **Depression** (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse | | ✓ | |
| **Dystonia:** twisting movements that you cannot control and can affect posture or the face including eyes, mouth, tongue or jaw, tightness of the throat, difficulty swallowing or breathing which may lead to choking | | ✓ | |
| **Extrapyramidal symptoms** (movement disorder): feeling restless, tense, involuntary muscle contractions, continuous spasms, rigidity, slowness of movement, tremor, jerky movements, abnormal walking pattern | | ✓ | |
| **Hallucinations** (seeing or hearing things that are not there) | | ✓ | |
| **Hypertonia** (muscle tension): feeling tense, increased muscle tone or stiff muscles | | ✓ | |
| **New or worsening constipation** | | ✓ | |
| **Tachycardia** (abnormally fast heartbeat): Sensation of rapid, pounding heart beat, dizziness, shortness of breath | | ✓ | |
| **Uncommon** | | | |
| **Dyskinesia:** involuntary movements that you can't control, | | ✓ | |

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| muscle spasms, or muscle twitching | | | |
| **Hypotension** (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up) | | ✓ | |
| **Oculogyric crisis** (neurological disorder): involuntary, often upward, eye muscle spasms | | | ✓ |
| **Seizures** (fits): loss of consciousness with uncontrollable shaking | | | ✓ |
| **Tardive dyskinesia:** muscle twitching or abnormal movement of your face or tongue or other parts of your body | | ✓ | |
| **Rare** | | | |
| **Anaphylactic reaction** (severe allergic reaction)**:** difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat | | | ✓ |
| **Diabetic ketoacidosis (DKA):** difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, thirst, unusual fatigue, sleepiness or tiredness, a sweet or metallic taste in the mouth, sweet smelling breath, or different odour to urine or sweat | | | ✓ |
| **Hyperglycemia** (high blood sugar)**:** increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue | | ✓ | |
| **Hyperprolactinemia** (elevated prolactin levels): irregular menstrual cycles, production and discharge of breast milk, abnormal hair growth, infertility | | ✓ | |
| **Leukopenia** (Low white blood cells): infections, fatigue, fever, | | | ✓ |

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| aches, pains, and flu-like symptoms | | | |
| **Neuroleptic malignant syndrome (NMS)**: severe muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness | | | ✓ |
| **Priapism**: long-lasting (greater than 4 hours in duration) and painful erection of the penis | | | ✓ |
| **QT prolongation** (a heart rhythm condition): irregular heartbeat, dizziness, fainting, seizures | | | ✓ |
| **Stroke** (bleeding or blood clot in the brain): sudden weakness or numbness of the face, arms, or legs and speech or vision problems | | | ✓ |
| **Very rare** | | | |
| **Liver disorder**: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite | | ✓ | |
| **Venous thromboembolism** (blood clots)**:** swelling, pain and redness in an arm or leg that is warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations | | | ✓ |
| **Unknown** | | | |
| **Dysphagia**: tightness of the throat, difficulty swallowing which may lead to choking or breathing difficulty | | | ✓ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting side effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- CLOPIXOL tablets should be stored in a safe place, between 15°C and 25°C. Safely discard any CLOPIXOL tablets you no longer use or that have passed the expiry date on the label. Ask your pharmacist how to properly dispose of them.
- CLOPIXOL ACUPHASE and CLOPIXOL DEPOT will be stored by your healthcare professional between 15°C and 25°C, protected from light.
- Keep out of reach and sight of children.

**If you want more information about CLOPIXOL, CLOPIXOL ACUPHASE and CLOPIXOL DEPOT:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or the manufacturer's website http://www.lundbeck.ca, or by calling 1-800-586-2325.
- This information is current up to the time of the last authorization date shown below, but more current information may be available from the manufacturer.

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