PROFESSIONAL INFORMATION/PACKAGE INSERT
CLOPIXOL ACUPHASE® INJECTION

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

CLOPIXOL ACUPHASE 50 mg/ml Injection

COMPOSITION:

CLOPIXOL ACUPHASE Injection is a sterile solution of zuclopenthixol acetate in an oily vehicle intended for intramuscular injection.

1 ml ampoule: Zuclopenthixol acetate 50 mg/ml

The other ingredient is triglycerides, medium chain.

CATEGORY AND CLASS:

A 2.6.5 Thioxanthenes

PHARMACOLOGICAL ACTION:

CLOPIXOL ACUPHASE induces a transient dose-dependent sedation. The unspecific sedation appears rapidly after administration of the injection, is significant within 2 hours and reaches its maximum within approximately 8 hours, whereupon it declines substantially and remains weak in spite of repeated injection. The duration of action is 2 to 3 days.

By esterification of zuclopenthixol with acetic acid, zuclopenthixol has been converted to a more lipophilic substance, zuclopenthixol acetate. When dissolved in oil (CLOPIXOL ACUPHASE) and injected intramuscularly, this substance diffuses rather slowly into the surrounding body water, where it undergoes enzymatic breakdown to release the active component zuclopenthixol.

Maximum serum concentration of zuclopenthixol is reached on an average of 36 hours after an injection, then the serum curve declines rather slowly. Three days after the injection the serum level is about one third of the maximum.

Zuclopenthixol is distributed in the organism with the highest concentration of drug and metabolites occurring in liver, lungs, intestines and kidneys and lower concentrations in heart, spleen, brain and blood. The apparent volume of distribution is about 20 l/kg and the protein binding about 98%.

Zuclopenthixol crosses the placental barrier in small amounts. Zuclopenthixol is excreted in breast milk in small amounts - the milk concentration/serum concentration ratio in women is on an average 0,3.

The metabolism of zuclopenthixol proceeds along three main routes:
Sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are psychopharmacologically inactive. Excretion occurs mainly via the faeces, with some degree of urinary excretion. The systemic clearance is about 0,9 l/minute.

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

INDICATIONS:

Initial treatment of acute psychoses, including mania, exacerbations of chronic psychoses.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients, listed under **Composition**.

Acute alcohol, barbiturate and opiate intoxications, comatose states

Safety and efficacy have not been established in children

WARNINGS AND SPECIAL PRECAUTIONS:

Neuroleptic malignant syndrome may occur. Symptoms may be: hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system.

Treatment:

- Discontinuation of CLOPIXOL ACUPHASE.
- Symptomatic treatment and use of general supportive measures.
- Dantrolene and bromocriptine may be helpful.

Symptoms may persist for more than a week after oral neuroleptics are discontinued and somewhat longer when associated with the depot forms of the agents.

CLOPIXOL ACUPHASE should be used with caution in patients with, convulsive disorders or advanced hepatic, renal or cardiovascular disease.

CLOPIXOL ACUPHASE should not be administered during pregnancy and lactation (See **Human Reproduction**).

CLOPIXOL ACUPHASE may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

CLOPIXOL ACUPHASE may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of cardiac dysrhythmias, resulting in an increased risk of death. Therefore, CLOPIXOL ACUPHASE should be used with caution in susceptible individuals (with hypokalemia, hypomagnesaemia 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 dysrhythmia. Concomitant treatment with other antipsychotics should be avoided (see **Interactions**).

Cases of venous thromboembolism (VTE) have been reported. All possible risk factors for VTE should be identified before and during treatment with CLOPIXOL ACUPHASE and preventive measures undertaken.

Older people

Cerebrovascular

An approximately 3-fold increased risk of cerebrovascular accident (stroke) has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations.
CLOPIXOL ACUPHASE should be used with caution in patients with risk factors for stroke.

Increased Mortality in Older people with Dementia

Data from two large observational studies showed that older people with dementia who are treated with antipsychotics are at an increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

CLOPIXOL ACUPHASE is not licensed for the treatment of dementia-related

behavioural disturbances.

Effects on ability to drive and use machines

The ability to drive or operate machinery may be affected. Therefore, caution should be exercised initially, until the individual reaction to the treatment is known.

INTERACTIONS:

Combinations requiring precautions for use

CLOPIXOL ACUPHASE enhances the response to alcohol and the effects of barbiturates and other central nervous system depressants.

CLOPIXOL ACUPHASE should not be given concomitantly with guanethidine or similar acting compounds, since neuroleptics may block the antihypertensive effect of these compounds.

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

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of one another.

CLOPIXOL ACUPHASE may reduce the effect of levodopa and the effect of adrenergic agents.

Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal symptoms.

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

Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co-administration of other agents known to significantly increase the QT interval. Co-administration of such agents should be avoided. Relevant classes include:

- class Ia and III antidysrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)

- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

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

Medicines known to cause electrolyte disturbances such as thiazide diuretics (hypokalemia) and medicines known to increase the plasma concentration of zuclopenthixol acetate should also be used with caution as they may increase the risk of QT prolongation and cardiac dysrhythmias resulting in an increased risk of death. (see **Warnings and Special Precautions**).

HUMAN REPRODUCTION:

Pregnancy

CLOPIXOL ACUPHASE should not be administered during pregnancy and lactation. (see **Warnings and Special Precautions**).

Neonates exposed to CLOPIXOL ACUPHASE during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation

Zuclopenthixol is excreted into breast milk. Mothers on CLOPIXOL ACUPHASE therapy should not breastfeed their babies.

Fertility

In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported (see **Side Effects**). These events may have a negative impact on female and/or male sexual function and fertility.

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

Administration of CLOPIXOL to male and female rats were associated with a slight delay in mating. In an experiment where CLOPIXOL was administered via the diet, impaired mating performance and reduced conception rate was noted.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

Dosage should be individually adjusted according to the patient's condition. CLOPIXOL ACUPHASE is administered by intramuscular injection.

The dose range would normally be 50 - 150 mg (1 - 3 ml) i.m., repeated if necessary, preferably with a time interval of 2 to 3 days. In a few patients an additional injection may be needed 24 to 48 hours following the first injection.

In the maintenance therapy, treatment should be continued with CLOPIXOL DEPOT i.m. according to the following guidelines:

Change to maintenance treatment with CLOPIXOL DEPOT:

Concomitantly with the last injection of CLOPIXOL ACUPHASE 200 - 400 mg (1 - 2 ml) of CLOPIXOL DEPOT should be given intramuscularly and repeated every 2nd week. Higher doses or shorter intervals may be needed.

SIDE EFFECTS:

The following side effects have been reported:

Extrapyramidal reactions may occur. Tardive dyskinesias may develop.

In the listing below a Frequent event is defined as either a very common or common event (>1/100); all other events are defined as Less frequent.

Organ class	**Frequency**	**Preferred term**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction.
Endocrine disorders	Less frequent	Hyperprolactinaemia.
Metabolism and nutrition disorders	Frequent	Increased appetite, weight increased.
	Less frequent	Decreased appetite, weight decreased ,hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.
Psychiatric disorders	Frequent	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Less frequent	Apathy, nightmare, libido increased, confusional state.
Nervous system disorders	Frequent	Somnolence, akathisia, hyperkinesia, hypokinesia, tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.

	Less frequent	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine, Neuroleptic malignant syndrome.
Eye disorders	Frequent	Accommodation disorder, abnormal vision.
	Less frequent	Oculogyration, mydriasis.
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Hyperacusis, tinnitus.
Cardiac disorders	Frequent	Tachycardia, palpitations.
	Less frequent	Electrocardiogram QT prolonged.
Vascular disorders	Less frequent	Hypotension, hot flush, venous thromboembolism.
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Frequent	Dry mouth, salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Less frequent	Abdominal pain, nausea, flatulence
Hepato-biliary disorders	Less frequent	Liver function test abnormal, cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, pruritus.
	Less frequent	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Frequent	Myalgia.
	Less frequent	Muscle rigidity, trismus, torticollis.
Renal and urinary disorders	Frequent	Micturition disorder, urinary retention, polyuria.
Pregnancy, puerperium and perinatal conditions	Less frequent	Drug withdrawal syndrome neonatal (see Human reproduction Pregnancy).
Reproductive system and breast disorders	Less frequent	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness, gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site	Frequent	Asthenia, fatigue, malaise, pain.
	Less frequent	Thirst, injection site reaction,

conditions		hypothermia, pyrexia.

Cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for CLOPIXOL ACUPHASE (see **Warnings and Special Precautions**).

Abrupt discontinuation of CLOPIXOL ACUPHASE 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.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS

OF ITS TREATMENT:

Symptoms:

Somnolence, coma extrapyramidal symptoms, convulsions, shock, hyper – or hypothermia. ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when CLOPIXOL ACUPHASE is administered in overdose together with medicines known to affect the heart.

Treatment

Treatment is symptomatic and supportive. Measures aimed at supporting the respiratory and cardiovascular systems should be instituted. Adrenaline (epinephrine) must not be used in these patients.

IDENTIFICATION:

Clear, yellowish, oil, practically free form particles.

PRESENTATION:

1 x 1 ml ampoule

STORAGE INSTRUCTIONS:

Store at or below 30 ºC

Keep the ampoules in the outer carton to protect from light.

Keep out of reach of children.

REGISTRATION NUMBER:

W/2.6.5/27

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION:

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