

IL-604904

Physician Package Insert

**Clopixol-Acuphase®****50 mg/ml**

Zuclopendixol acetate

**SUMMARY OF PRODUCT CHARACTERISTICS****1. NAME OF THE MEDICINAL PRODUCT**

Clopixol-Acuphase 50 mg/ml

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Zuclopendixol acetate 50 mg/ml

For a full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**Solution for injection (I.M.).  
Clear, yellowish oil, practically free from particles.**4. CLINICAL PARTICULARS****4.1 Therapeutic indications**

Acute psychoses.

**4.2 Posology and method of administration***Adults*

Dosage should be individually adjusted according to the condition of the patient.

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.

Zuclopendixol acetate is not intended for long-term use and duration of treatment should not be more than two weeks. The maximum accumulated dosage in a course should not exceed 400 mg and the number of injections should not exceed four.

In the maintenance therapy, treatment should be continued with oral zuclopendixol or zuclopendixol decanoate i.m., after the following guidelines:

**1) Change to oral zuclopendixol**

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

**2) Change to zuclopendixol decanoate**

Concomitantly with the (last) injection of zuclopendixol acetate (100 mg), 200-400 mg (1-2 ml) of zuclopendixol decanoate 200 mg/ml should be given intramuscularly and repeated every 2nd week. Higher doses or shorter intervals may be needed.

Zuclopendixol acetate and zuclopendixol decanoate can be mixed in a syringe and given as one injection (co-injection).

Subsequent doses of zuclopendixol decanoate and interval between injections should be adjusted according to the response of the patient.

*Elderly patients*

The dosage may need to be reduced in the elderly. Maximum dosage per injection should be 100 mg.

*Children*

Clopixol-Acuphase is not recommended for use in children due to lack of clinical experience.

*Reduced renal function*

Clopixol-Acuphase can be given in usual doses to patients with reduced renal function.

*Reduced liver function*

Patients with compromised hepatic function should receive half the recommended dosages and, if possible, a serum level determination is advisable.

*Method of administration*

Clopixol-Acuphase is administered by intramuscular injection into the upper outer quadrant of the gluteal region. Injection volumes exceeding 2 ml should be distributed between two injection sites. Local tolerability is good.

*Note:* As with all oil injections it is important to ensure, by aspiration before injection, that inadvertent intravascular entry does not occur.**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients, (see section 6.1).

Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma.

**4.4 Special warnings and precautions for use**

The possibility of development of neuroleptic malignant syndrome (hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system) exists with any neuroleptic. The risk is possibly greater with the more potent agents. Patients with pre-existing organic brain syndrome, mental retardation and opiate and alcohol abuse are over-represented among fatal cases.

Treatment: Discontinuation of the neuroleptic. 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 drugs.

Like other neuroleptics zuclopendixol acetate should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic disease.

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

As with other drugs belonging to the therapeutic class of antipsychotics, zuclopendixol acetate may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, zuclopendixol acetate should be used with caution in susceptible individuals (with hypokalemia, hypomagnesemia or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (&lt;50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with zuclopendixol acetate and preventive measures undertaken.

*Elderly**Cerebrovascular*

An approximately 3-fold increased risk of cerebrovascular adverse events have 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. Zuclopendixol acetate should be used with caution in patients with risk factors for stroke.

*Increased Mortality in Elderly people with Dementia*

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

Zuclopendixol acetate is not licensed for the treatment of dementia-related behavioural disturbances.

**4.5 Interaction with other medicinal products and other forms of interaction***Combinations requiring precautions for use*

Zuclopendixol acetate may enhance the sedative effect of alcohol and the effects of barbiturates and other CNS depressants.

Neuroleptics may increase or reduce the effect of antihypertensive drugs; the antihypertensive effect of guanethidine and similar acting compounds is reduced.

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

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

Zuclopendixol acetate may reduce the effect of levodopa and the effect of adrenergic drugs.

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

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

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

- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. terfenadine, astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

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

Drugs known to cause electrolyte disturbances such as thiazidediuretics (hypokalemia) and drugs known to increase the plasma concentration of zuclopendixol acetate should also be used with caution as they may increase the risk of QT prolongation and malignant arrhythmias (see section 4.4).

**4.6 Pregnancy and lactation***Pregnancy*

Zuclopendixol acetate should not be administered during pregnancy unless the expected benefit to the patient outweighs the theoretical risk to the foetus.

The newborns of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyperexcitability and have a low apgar score.

Animal-reproduction studies on zuclopendixol have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproduction process.

*Lactation*

As zuclopendixol is found in breast milk in low concentrations it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is less than 1% of the weight related maternal dose (in mg/kg). Breast-feeding can be continued during zuclopendixol acetate therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

**4.7 Effects on ability to drive and use machines**

Clopixol Acuphase is a sedative drug. Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

**4.8 Undesirable effects**

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

Extrapyramidal reactions may occur, especially during the first few days after an injection and in the early phase 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 zuclopendixol therapy is recommended. In persistent akathisia a benzodiazepine or propranolol may be useful.

Frequencies are taken from the literature and spontaneous reporting. Frequencies are defined as: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10000$  to  $< 1/1000$ ), very rare ( $< 1/10000$ ), or not known (can not be estimated from the available data).

Cardiac disorders	Common	Tachycardia, palpitations.
	Rare	Electrocardiogram QT prolonged.
Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
Nervous system disorders	Very common	Somnolence, akathisia, hyperkinesia, hypokinesia.
	Common	Tremor, dystonia, hypertonia, dizziness, headache, paraesthesia, disturbance in attention, amnesia, gait abnormal.
	Uncommon to Rare	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, convulsion, migraine.
	Very rare	Neuroleptic malignant syndrome.
Eye disorders	Common	Accommodation disorder, vision abnormal.
	Uncommon	Oculogyration, mydriasis.
Ear and labyrinth disorders	Common	Vertigo.
	Uncommon	Hyperacusis, tinnitus.
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Very common	Dry mouth.
	Common	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Uncommon	Abdominal pain, nausea, flatulence.
Renal and urinary disorders	Common	Micturition disorder, urinary retention, polyuria.
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis, pruritus.
	Uncommon	Rash, photosensitivity reaction, pigmentation disorder, seborrhoea, dermatitis, purpura.
Musculoskeletal and connective tissue disorder	Common	Myalgia.
	Uncommon	Muscle rigidity, trismus, torticollis.
Endocrine disorders	Rare	Hyperprolactinaemia.

**TEXT  
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Notice: Colour matching of this print is only to be used as a guideline.

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Metabolism and nutrition disorders	Common	Increased appetite, weight increased.
	Uncommon	Decreased appetite, weight decreased.
	Rare	Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.
Vascular disorders	Uncommon	Hypotension, hot flush.
	Very rare	Venous thromboembolism
General disorders and administration site conditions	Common	Asthenia, fatigue, malaise, pain.
	Uncommon	Thirst, injection site reaction, hypothermia, pyrexia.
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction.
Hepatobiliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Cholestatic hepatitis, jaundice.
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state.

As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for zuclophenixol acetate (see section 4.4).

Abrupt discontinuation of zuclophenixol acetate 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.

#### 4.9 Overdose

Due to the administration form overdose symptoms are unlikely to occur.

#### Symptoms

Somnolence, coma, movement disorders, convulsions, shock, hyperthermia/hypothermia.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when administered in overdose together with drugs known to affect the heart.

#### Treatment

Treatment is symptomatic and supportive. Measures to support the respiratory and cardiovascular systems should be instituted. Epinephrine (adrenaline) should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and movement disorders with biperiden.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group*  
Neuroleptics (antipsychotics)  
ATC-code: N 05 AF 05

#### Mechanism of action

Zuclophenixol is a neuroleptic of the thioxanthene group.

The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect but possibly also 5 HT (5-hydroxytryptamine) receptor blockade contributes.

*In vitro* zuclophenixol has high affinity for both dopamine D<sub>1</sub> and D<sub>2</sub> receptors, for α<sub>1</sub>-adrenoceptors and 5 HT<sub>2</sub> receptors but no affinity for cholinergic muscarinic receptors. It has weak histamine (H<sub>1</sub>) receptor affinity and no α<sub>2</sub>-adrenoceptor blocking activity.

*In vivo* the affinity for D<sub>2</sub> binding sites dominates over the affinity for D<sub>1</sub> receptors. Zuclophenixol has proven to be a potent neuroleptic in all the behavioural studies for neuroleptic (dopamine receptor blocking) activity. Correlation is found in the *in vivo* test models, the affinity for dopamine D<sub>2</sub> binding sites *in vitro* and the average, daily oral antipsychotic doses.

Like most other neuroleptics zuclophenixol increases the serum prolactin level.

Pharmacological studies showed a pronounced effect 4 hours after parenteral application of zuclophenixol acetate in oil. Somewhat more marked effect was recorded in the period one to three days after the injection. During the following days the effect declined rapidly.

#### Clinical efficacy

In clinical use zuclophenixol acetate is intended for the initial treatment of acute psychoses, mania and exacerbation of chronic psychoses.

A single injection of zuclophenixol acetate ensures a pronounced and rapid reduction of psychotic symptoms. The duration of action is 2 to 3 days and normally only one or two injections are sufficient before the patients can be switched to oral or depot treatment.

Besides causing a significant reduction or complete elimination of the nuclear symptoms of schizophrenia such as hallucinations, delusions and thought disturbances zuclophenixol also has a marked effect on accompanying symptoms like hostility, suspiciousness, agitation and aggressiveness.

Zuclophenixol induces a transient dose-dependent sedation. However, such an initial sedation is usually advantageous in the acute phase of the psychosis as it calms the patient in the period before the antipsychotic effect sets in. The unspecific sedation is present rapidly after the injection, is significant after 2 hours and reaches its maximum in about 8 hours, whereupon it declines substantially and remains weak in spite of repeated injection.

Zuclophenixol acetate is particularly useful in the treatment of psychotic patients, who are agitated, restless, hostile, or aggressive.

#### 5.2 Pharmacokinetic properties

##### Absorption

By esterification of zuclophenixol with acetic acid zuclophenixol has been converted to a more lipophilic substance, zuclophenixol acetate. When dissolved in oil and injected intramuscularly the ester diffuses rather slowly from the oil to the body water phase where it is rapidly hydrolysed releasing the active zuclophenixol.

Following intramuscular injection maximum serum concentration is reached over a period of 24-48 hours (average 36 hours). The mean plasma elimination half-life (reflecting the release from the depot) is about 32 hours.

##### Distribution

The apparent volume of distribution (V<sub>d</sub>)<sub>B</sub> is about 20 l/kg. The plasma protein binding is about 98-99 %.

##### Biotransformation

The metabolism of zuclophenixol proceeds along three main routes - sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. Zuclophenixol dominates over metabolites in brain and other tissues.

##### Elimination

The elimination half-life (T<sub>1/2 β</sub>) of zuclophenixol is about 20 hours and the mean systemic clearance (Cl<sub>s</sub>) is about 0.86 l/min.

Zuclophenixol is excreted mainly with faeces, but also to some degree (about 10 %) with the urine. Only about 0.1 % of the dose is excreted unchanged with the urine, meaning that the drug load on the kidneys is negligible.

In nursing mothers zuclophenixol is excreted in small amounts with the breast milk. In steady state the pre-dose mean ratio milk conc./serum conc. in women treated orally or with the decanoate was about 0.29.

##### Linearity

The kinetics is linear. Average maximum serum level of zuclophenixol corresponding to a 100 mg dose of zuclophenixol acetate is 102 nmol/l (41 ng/ml). Three days after the injection the serum level is about one third of the maximum i.e. 35 nmol/l (14 ng/ml).

##### Elderly patients

The pharmacokinetic parameters are widely independent of the age of the patients.

##### Reduced renal function

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.

##### Reduced hepatic function

No data available.

##### Polymorphism

An *in vivo* investigation has shown that some part of the metabolic pathways is subject to genetic polymorphism of the sparteine/debrisoquine oxidation (CYP2D6).

### 5.3 Preclinical safety data

#### Acute toxicity

Zuclophenixol has low acute toxicity.

#### Chronic toxicity

In chronic toxicity studies there were no findings of concern for the therapeutic use of zuclophenixol.

#### Reproduction toxicity

Based on data from reproduction toxicity studies there is no reason to have special concern for the use of zuclophenixol in women of child bearing potential. However, in a peri/postnatal study in rats, dosages of 5 and 15 mg/kg/day resulted in an increase of stillbirths, reduced pup survival and delayed development of pups. The clinical significance of these findings is unclear and it is possible that the effect on pups was due to neglect from the dams that were exposed to doses of zuclophenixol producing maternal toxicity.

#### Mutagenicity and carcinogenicity

Zuclophenixol has no mutagenic or carcinogenic potential. In a rat oncogenicity study 30 mg/kg/day for two years (top dosage) resulted in slight non-statistical increases in the incidence of mammary adenocarcinomas, pancreatic islet cell adenomas, carcinomas in females, and thyroid parafollicular carcinomas. The slight increase in the incidence of these tumors is a common finding for D<sub>2</sub> antagonists, which increase prolactin secretion when administered to rats. 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.

#### Local toxicity

Local muscle damage is seen after injection of aqueous solutions of neuroleptics, including zuclophenixol. The muscle damage shows a much higher degree after the aqueous solutions of neuroleptics than after the oily solutions of zuclophenixol acetate and zuclophenixol decanoate.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Triglycerides, medium-chain.

#### 6.2 Incompatibilities

Zuclophenixol acetate should only be mixed with zuclophenixol decanoate, which also is dissolved in Triglycerides, medium-chain (Ph. Eur.).

Zuclophenixol acetate should not be mixed with depot formulations with sesame oil as the vehicle because this would result in definite changes in the pharmacokinetic properties of the involved preparations.

#### 6.3 Shelf life

2 years.

#### 6.4 Special precautions for storage

Store below 30°C.

Keep ampoules in the outer box in order to protect from light.

#### 6.5 Nature and contents of container

Colourless ampoules (Type I glass) of 1 ml and 2 ml.

Boxes of 1×1 ml, 5×1 ml and 10×1 ml and 1×2 ml, 5×2 ml and 10×2 ml.

Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

### 7. MANUFACTURER

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### 8. LICENSE NUMBER

047 80 25490

### 9. LICENSE HOLDER

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