Zuclopenthixol acetate

Clopixol-Acuphase®

50mg/ml solution for injection

1 NAME OF THE MEDICINAL PRODUCT

Zuclopenthixol acetate (Clopixol-Acuphase) 50 mg/mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zuclopenthixol acetate 50 mg/ml

For the full list of excipients, see section 7.1.

3 PHARMACOLOGIC CATEGORY

Antipsychosis (Neuroleptic)

4 PHARMACEUTICAL FORM

Solution for injection.

Clear, yellowish oil, practically free from particles.

5 CLINICAL PARTICULARS

5.1 Therapeutic indications

Initial treatment of acute psychoses, including mania, and exacerbation of chronic psychoses.

5.2 Posology and method of administration

Posology

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.

Zuclopenthixol 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 zuclopen-thixol or zuclopenthixol decanoate i.m., after the following guidelines:

1) Change to oral zuclopenthixol
2 to 3 days after the last injection of zuclopenthixol acetate a patient who has been treated with 100 mg zuclopenthixol 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 zuclopenthixol decanoate
Concomitantly with the (last) injection of zuclopenthixol acetate (100 mg), 200-400 mg (1-2 ml) of zuclopenthixol decanoate 200 mg/ml should be given intramuscularly and repeated every 2nd week. Higher doses or shorter intervals may be needed.

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

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

Older patients

The dosage may need to be reduced in the older. 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.

5.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients, listed in section 7.1.

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

5.4 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 discon-tinued and somewhat longer when associated with the depot forms of the drugs.

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

As described for other psychotropics zuclopenthixol 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, zuclo-penthixol acetate may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, zuclopenthixol acetate 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 (see section 5.5).

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 zuclopenthixol acetate and preventive measures undertaken.

Older people
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. Zuclopenthixol acatate 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 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.

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

5.5 Interaction with other medicinal products and other forms of interaction

Combinations requiring precautions for use
Zuclopenthixol 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. Zuclopenthixol 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 zuclopenthixol is partly metabolised by CYP2D6 concomitant use of drugs 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 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 thiazidediuretica (hypoka-lemia) and drugs 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 malignant arrhythmias (see section 5.4).

5.6 Fertility, pregnancy and lactation

Pregnancy

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

Neonates exposed to antipsychotics (including zuclopenthixol acetate) during the third trimester of pregnancy are at risk of adverse reactions including extrapy-ramidal 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.

Animal studies have shown reproductive toxicity (see section 6.3).

Breast-feeding

As zuclopenthixol 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 zuclopenthixol acetate therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

Fertility

In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenor-rhoea, erectile dysfunction and ejaculation failure have been reported (see section 5.8). 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 zuclopenthixol to male and female rats were 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.

5.7 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.

5.8 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 zuclopenthixol 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), or not known (can not be estimated from the available data).

Blood and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction.
Endocrine disorders	Rare	Hyperprolactinaemia.
Metabolism and nutrition disorders	Common	Increased appetite, weight increased.
	Uncommon	Decreased appetite, weight decreased.
	Rare	Hyperglycaemia, glucose tolerance impaired, hyperlipidaemia.
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state.
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.
Cardiac disorders	Common	Tachycardia, palpitations.
	Rare	Electrocardiogram QT prolonged.

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NEW MATERIAL
Material No.: 151637
Punch: 0660
Size/mm.: 190x600
PCR/CR No.: 932692

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Black

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

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Vascular disorders	Uncommon	Hypotension, hot flush.
	Very rare	Venous thromboembolism
Respiratory, thoracic and medistianal disorders	Common	Nasal congestion, dyspnoea.
Gastrointestinal disorders	Very common	Dry mouth.
	Common	Salivary hypersecretion, constipation, vomiting, dyspepsia, diarrhoea.
	Uncommon	Abdominal pain, nausea, flatulence.
Hepato-biliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Cholestatic hepatitis, jaundice.
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.
Renal and urinary disorders	Common	Micturition disorder, urinary retention, polyuria.
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal (see 5.6)
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders and administration site conditions	Common	Asthenia, fatigue, malaise, pain.
	Uncommon	Thirst, injection site reaction, hypothermia, pyrexia.

As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for zuclopenthixol acetate (see section 5.4).

Abrupt discontinuation of zuclopenthixol 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare
professionals are asked to report any suspected adverse reactions via the national reporting system

Center for Drug Regulation & Research (CDRR)
Food and Drug Administration
Civic Drive, Filinvest Corporate City,
Alabang, Muntinlupa City
Philippines
Tel. no. (+632) 857-1990
Email: info@fda.gov.ph
Website: http://www.fda.gov.ph

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

Symptoms
Somnolence, coma, movement disorders, convulsions, shock, hyperther-mia/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.

6 PHARMACOLOGICAL PROPERTIES

6.1 Pharmacodynamic properties
Pharmacotherpeutic group Neuroleptics (antipsychoics)
ATC-code: N 05 AF 05

Mechanism of action
Zuclopenthixol 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 zuclopenthixol has high affinity for both dopamine D1 and D2 receptors, for α1-adrenoceptors and 5-HT2 receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H1) receptor affinity and no α2-adrenoceptor blocking activity.

In vivo the affinity for D2 binding sites dominates over the affinity for D1 receptors. Zuclopenthixol 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 D2 binding sites in vitro and the average, daily oral antipsychotic doses.

Like most other neuroleptics zuclopenthixol increases the serum prolactin level. Pharmacological studies showed a pronounced effect 4 hours after parenteral application of zuclopenthixol 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 and safety
In clinical use zuclopenthixol acetate is intended for the initial treatment of acute psychoses, mania and exacerbation of chronic psychoses.

A single injection of zuclopenthixol 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 zuclopenthixol also has a marked effect on accompanying symptoms like hostility, suspiciousness, agitation and aggressiveness.

Zuclopenthixol 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.

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

6.2 Pharmacokinetic properties
Absorption
By esterification of zuclopenthixol with acetic acid zuclopenthixol has been converted to a more lipophilic substance, zuclopenthixol 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 zuclopenthixol.

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 (Vd)β is about 20 l/kg. The plasma protein binding is about 98-99 %.

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

Elimination
The elimination half-life (T½ β) of zuclopenthixol is about 20 hours and the mean systemic clearance (Cls) is about 0.86 l/min.

Zuclopenthixol 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 zuclopenthixol 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 zuclopenthixol corresponding to a 100 mg dose of zuclopenthixol 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).

Older 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).

6.3 Pre-clinical safety data
Acute toxicity
Zuclopenthixol has low acute toxicity.

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

Reproductive toxicity
In a three-generation study in rats a delay in mating was noted. Once mated there was no effect on fertility. In an experiment where zuclopenthixol was administered via the diet, impaired mating
performance and reduced conception rate was noted.

Animal reproduction studies have not shown evidence of embryotoxic or teratogenic effects.

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 maternal neglect at doses of zuclopenthixol producing maternal toxicity.

Mutagenicity and carcinogenicity
Zuclopenthixol has no mutagenic or carcinogenic potential. In a rat oncogenecity 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 D2 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 zuclopenthixol. The muscle damage shows a much higher degree after the aqueous solutions of neuroleptics than after the oily solutions of zuclopenthixol acetate and zuclopenthixol decanoate.

7 PHARMACEUTICAL PARTICULARS

7.1 List of excipients
Triglycerides, medium-chain.

7.2 Incompatibilities
Zuclopenthixol acetate should only be mixed with zuclopenthixol decanoate, which also is dissolved in Triglycerides, medium-chain.

Zuclopenthixol 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.

7.3 Shelf life
2 years.

7.4 Special precautions for storage
Do not store above 30°C
Keep ampoules in the outer box in order to protect from light.

7.5 Nature and contents of container
Colourless ampoules (Type I glass) of 1 ml

Boxes of 5×1 ml.

7.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph Patient is advised to seek medical attention immediately at first sign of any adverse drug reaction.

8 MARKETING AUTHORISATION HOLDER

Manufacturer
H. Lundbeck A/S
Ottiliavej 9
Valby, 2500, Denmark

Imported and Distributed by:
METRO DRUG,INC.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna,
Philippines

9 MARKETING AUTHORISATION NUMBER(S)

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