SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, yellowish oil, practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute psychoses.

4.2 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 zuclopenthixol 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.
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 listed in 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

Caution should be exercised in patients having: liver disease; cardiac disease, or arrhythmias; severe respiratory disease; renal failure; epilepsy (and conditions predisposing to epilepsy, e.g. alcohol withdrawal or brain damage); Parkinson's disease; narrow angle glaucoma; prostatic hypertrophy; hypothyroidism; hyperthyroidism; myasthenia gravis; phaeochromocytoma and patients who have shown hypersensitivity to thioxanthenes or other antipsychotics.

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, zuclopenthixol acetate should be used with caution in patients with organic brain syndrome, convulsions or advanced hepatic, renal or cardiovascular disease.

Blood dyscrasias have been reported rarely. Blood counts should be carried out if a patient develops signs of persistent infection.

As with other drugs belonging to the therapeutic class of antipsychotics, zuclopenthixol 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 hypokalaemia, 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 arrhythmia.

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.

Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

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

Older people

Older people require close supervision because they are especially prone to experience such adverse effects as sedation, hypotension, confusion, and temperature changes.

Cerebrovascular

An approximately 3-fold increased risk of cerebrovascular adverse events 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.

Zuclopenthixol acetate 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 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.

Clopixol-Acuphase is not licensed for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antipsychotics, zuclopenthixol enhances the response to alcohol, the effects of barbiturates and other CNS depressants.

Zuclopenthixol may potentiate the effects of general anaesthetics and anticoagulants and prolong the action of neuromuscular blocking agents.

The anticholinergic effects of atropine or other drugs with anticholinergic properties may be increased.

Concomitant use of drugs such as metoclopramide, piperazine or antiparkinson drugs may increase the risk of extrapyramidal effects such as tardive dyskinesia.

Combined use of antipsychotics and lithium or sibutramine has been associated with an increased risk of neurotoxicity.

Antipsychotics may enhance the cardiac depressant effects of quinidine; the absorption of corticosteroids and digoxin.

The hypotensive effect of vasodilator antihypertensive agents such as hydralazine and α blockers (e.g. doxazosin), or methyl-dopa may be enhanced.

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
- some quinolone antibiotics (e.g. 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 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 (see section 4.4).

Antipsychotics may antagonise the effects of adrenaline and other sympathomimetic agents, and reverse the antihypertensive effects of guanethidine and similar adrenergic-blocking agents.

Antipsychotics may also impair the effect of levodopa, adrenergic drugs and anticonvulsants.

The metabolism of tricyclic antidepressants may be inhibited and the control of diabetes may be impaired.

Since zuclopenthixol is partly metabolised by CYP2D6 concomitant use of drugs known to inhibit this enzyme may lead to higher than expected plasma concentrations of zuclopenthixol, increasing the risk of adverse effects and cardiotoxicity.

4.6 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 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.

Animal studies have shown reproductive toxicity (see section 5.3).

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, amenorrhoea, erectile dysfunction and ejaculation failure have been reported (see section 4.8). These events may have a negative impact on female and/or male sexual function and fertility.

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.

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.

4.7 Effects on ability to drive and use machines

Zuclopenthixol is a sedative drug.

Alertness may be impaired, especially at the start of treatment, or following the consumption of alcohol; patients should be warned of this risk and advised not to drive or operate machinery until their susceptibility is known.

Patients should not drive if they have blurred vision.

4.8 Undesirable effects

The majority of undesirable effects are 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 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 it. 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.
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 4.6)
Reproductive system and breast disorders	Uncommon	Ejaculation failure, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness.
	Rare	Gynaecomastia, galactorrhoea, amenorrhoea, priapism.
General disorders	Common	Asthenia, fatigue, malaise, pain.

and administration site conditions	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 (see section 4.4).

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

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**.**

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdose

Symptoms: somnolence, coma, extrapyramidal symptoms, convulsions, hypotension, shock, hyper or 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 aimed at supporting the respiratory and cardiovascular systems should be instituted. Adrenaline (epinephrine) must not be used in these patients. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Neuropleptics (antipsychotics), ATC Code: N05AF05

Mechanism of action

Zuclopenthixol is a potent neuroleptic of the thioxanthene series with a piperazine side-chain. The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect. The thioxanthenes have a high affinity for both the adenylate cyclase coupled dopamine D1 receptors and for the dopamine D2 receptors; in the phenothiazine group the affinity for D1 receptors is much lower than that for D2 receptors, whereas butyrophenones, diphenylbutylpiperidines and benzamides only have affinity for D2 receptors.

In the traditional tests for antipsychotic effect, e.g. antagonism of stereotypic behaviour induced by dopamine agonists, the chemical groups of neuroleptics mentioned reveal equal but dosage dependent activity. However, the antistereotypic effect of phenothiazines, butyrophenones, diphenylbutylpiperidines, and benzamindes is strongly counteracted by the anticholinergic drug, scopolamine, while the antisteriotypic effect of the thioxanthenes, e.g. zuclopenthixol, is not, or only very slightly, influenced by concomitant treatment with anticholinergics.

5.2. Pharmacokinetic Properties

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 this substance diffuses slowly into the surrounding body water, where enzymatic breakdown occurs releasing the active component zuclopenthixol.

Maximum serum concentrations of zuclopenthixol are usually reached 36 hours after an injection, after which the serum levels decline slowly. The average maximum serum level corresponding to the 100 mg dose is 41 ng/mL. Three days after the injection the serum level is about one third of the maximum.

Zuclopenthixol is distributed in the body in a similar way to other neuroleptics; with the higher concentrations of drug and metabolites 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 small amounts with the milk - the ratio milk concentration/serum concentration in women is on average 0.3.

The metabolism of zuclopenthixol proceeds via three main routes -sulphoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. The excretion proceeds mainly with the faeces but also to some degree with the urine. The systemic clearance is about 0.9 L/min.

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

5.3 Preclinical safety data

Reproductive toxicity

Impaired mating performance and reduced conception rates were observed in rats treated with zuclopenthixol at doses equal to the maximum recommend human dose of 50 mg on a mg/m^2 basis.

There was no evidence of embryotoxicity or teratogenic effects in rats treated with zuclopenthixol, however adverse effects on pre-and postnatal development (i.e. increased stillbirths, reduced pup survival and delayed development of pups) was observed. 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.

Mutagenicity and carcinogenicity

Zuclopenthixol has no mutagenic potential. In a rat oncogenicity study, 30 mg/kg/day resulted in slight non statistical increases in the incidence of mammary adenocarcinomas and pancreatic islet cell adenomas and carcinomas in females of thyroid parafollicular carcinomas. This is a common finding for D2 antagonists which increase prolactin secretion when administered to rats. The physiological differences between rats and humans suggest that these changes are not predictive of an oncogenic risk in patients.

Local toxicity

Local muscle damage is less pronounced with oily solutions of zuclopenthixol (including Clopixol-Acuphase) then with aqueous solutions of zuclopenthixol and other neuroleptics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium-chain.

6.2 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.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

Keep the ampoules in the outer carton 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, 1×2 ml, 10×1 ml and 10×2 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MANUFACTURER

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8. REGISTRATION HOLDER

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9. REGISTRATION NUMBER(S)

047-80-25490

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