Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clopixol Acuphase 50 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains zuclopenthixol acetate 50mg in 1ml of injection fluid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
Clear, yellowish, oil, practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Initial treatment of acute psychoses including mania and exacerbation of chronic 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 two or thee days. In a few patients an additional injection may be needed 24 to 48 hours after 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., according to the following guidelines:

1) Change to oral zuclopenthixol
Two to three 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 two to three 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.

Elderly
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 hepatic function
Dose reduction (relative to the degree of hepatic impairment) should be considered. If possible, where assay facilities exist dosage should be adjusted according to serum levels.

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.

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
- Use in children
- Use in senile confusional states

4.4 Special warnings and precautions for use

Extrapyramidal reactions in the form of acute dystonias (including oculogyric crisis), parkinsonian rigidity, tremor, akinesia and akathisia have been reported and may occur even at lower dosage in susceptible patients. Such effects would usually be encountered early in treatment, but delayed reactions may also occur. Antiparkinson agents should not be prescribed routinely because of the possible risk of precipitating toxic-confusional states, impairing efficacy or causing anticholinergic side-effects. They should only be given if required and their requirement reassessed at regular intervals.

Tardive dyskinesia can occur with neuroleptic treatment. It is more common at high doses for prolonged periods but has been reported at lower dosage for short periods. The risk seems to be greater in the elderly, especially females. It has been reported that fine vermicular movements of the tongue are an early sign. It has been observed occasionally in patients receiving zuclopenthixol. The concurrent use of anticholinergic antiparkinson drugs may exacerbate this effect. The potential irreversibility and seriousness, as well as the unpredictability of the syndrome, requires especially careful assessment of the risk versus benefit, and the lowest possible dosage and duration of treatment consistent with therapeutic efficacy. Short-lived dyskinesia may occur after abrupt withdrawal of the drug.

The hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may be associated with galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea. Sexual function, including erection and ejaculation may be impaired; but increased libido has also been reported.

The possibility of development of neuroleptic malignant syndrome 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. Rare cases reported as NMS have also been received in association with zuclopenthixol. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, sweating and cardiac arrhythmia). Additional signs may include elevated creatinine, phosphokinase, myoglubinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all neuroleptic medication, including zuclopenthixol must be

discontinued. 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 antipsychotics zuclopenthixol acetate should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic disease.

Zuclopenthixol should also be used with caution in patients who are excitable or overactive, in patients with convulsive disorders, severe atherosclerosis, severe respiratory disease and Parkinson's disease. Care should also be taken in patients with personal or family history of narrow angle glaucoma.

Administration to patients with Parkinsonism or extrapyramidal disease may induce an exacerbation of that disorder.

As described for other psychotropics zuclopenthixol acetate may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.
The general caution for use of neuroleptics in hypothyroidism, thyrotoxicosis, myasthenia gravis or prostatic hypertrophy should be observed, but there is no evidence to suggest that zuclopenthixol gives rise to any particular problem in such conditions.

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

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 hypokalemia, hypomagnesaemia or family history of QT prolongation) 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 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 Clopixol and preventive measures undertaken.

Elderly
Care should also be taken in the elderly, particularly if frail or at risk of hypothermia, sedation, hypotension or confusion.

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 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.

Clopixol 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

Zuclopenthixol may enhance the sedative effect of alcohol, and the effects of barbiturates and other CNS depressants and may potentiate the effects of general anaesthetics.

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.

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.

Neuroleptics may enhance the absorption of corticosteroids and digoxin, the hypotensive effects of vasodilator antihypertensive agents such as hydralazine and prolong the action of neuromuscular blocking agents.

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

As for other atypical antipsychotics, caution is advised in patients taking zuclopenthixol in concomitant use with oral anticoagulants (e.g. warfarin), and other medicinal products known to affect platelet function (e.g. phenothiazines, most tricyclic antidepressants, acetylsalicyclic acid, and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole).

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 thiazide diuretics (hypokalaemia) 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 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with zuclopenthixol.

Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential 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 embryo-foetal developmental reproduction studies on zuclopenthixol have not given evidence of an increased incidence of foetal malformations or effects on embryo viability. An animal pre and post natal study showed an increase in stillbirths, reduced pup survival and delayed development of pups at dose levels causing maternal toxicity. The potential risk for humans is unknown.

Neonates exposed to antipsychotics (including zuclopenthixol) 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
As zuclopenthixol is found in breast milk in low concentrations, breast-feeding should not be continued during therapy unless in the opinion of the physician the expected benefit to the patient outweighs the potential risk to the infant.

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 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 (cannot 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.
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.
Hepato-biliary disorders	Uncommon	Liver function test abnormal.
	Very rare	Cholestatic hepatitis, jaundice.
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.
Psychiatric disorders	Common	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased.
	Uncommon	Apathy, nightmare, libido increased, confusional state.

Localised erythema, pruritus and injection site nodule are the most typical injection site reactions.
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 4.4).

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.

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 arrthymias 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. Adrenaline (epinephrine) 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
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 D_1 and D_2 receptors, for α_1-adrenoceptors and $5\text{−}HT_2$ receptors but no affinity for cholinergic muscarine receptors. It has weak histamine (H_1) receptor affinity and no α_2-adrenoceptor blocking activity.

In vivo the affinity for D_2 binding sites dominates over the affinity for D_1 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 D_2 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
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 two to three 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.

5.2 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 $(V_d)_\beta$ 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 ($T_{½\ \beta}$) of zuclopenthixol is about 20 hours and the mean systemic clearance (Cl_s) 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).

Elderly patients
The pharmacokinetic parameters are 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
Zuclopenthixol has low acute toxicity.

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

Reproduction toxicity
Zuclopenthixol was tested for developmental toxicity in rats and rabbits after oral administration. Under the conditions of the studies, zuclopenthixol did not induce malformations or affect embryo-foetal viability.

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 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 D_2 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products apart from other injections in the Clopixol range (see section 4.2).

6.3 Shelf life

2 years as packaged for sale.
Once opened use immediately and discard any unused solution.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

A clear glass (Type I Ph. Eur.) ampoule containing zuclopenthixol acetate 50mg in 1ml of thin vegetable oil.

The ampoules are packed in boxes of 5.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Lundbeck Ltd.
Lundbeck House
Caldecotte Lake Business Park
Caldecotte
Milton Keynes MK7 8LG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 115/5/9

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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