Clopixol Acutard

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINE

Clopixol Acutard 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

Injectable solution

A clear, light yellow solution, practically free of particles.

4. CLINICAL DATA

4.1 Therapeutic indications

Clopixol Acutard is advised as initial treatment for acute psychoses, manic states, and exacerbations of chronic psychoses if oral treatment is not possible.

4.2 Dosage and method of administration

Dosage

Adults:
The dose will depend on the patient's clinical condition.
The usual dosage is 50 to 150 mg (1 to 3 ml), administered exclusively by intramuscular injection. The injection may be repeated if necessary after an interval of 2 to 3 days. In some cases, the patient may require a second injection within 24 to 48 hours of the first injection.

Zuclopenthixol acetate is not indicated for long-term use, and the duration of treatment should not exceed two weeks. The maximum cumulative dose should not exceed 400 mg, and the number of injections should not exceed four.

Maintenance treatment will be administered either orally or by using zuclopenthixol decanoate intramuscularly, according to the following guidelines:

1) Switching to oral zuclopenthixol:
A patient treated with 100 mg of zuclopenthixol acetate should, 2 to 3 days after the last zuclopenthixol acetate injection, switch to an oral dose of approximately 40 mg/day, possibly divided into several doses. If necessary, the dose can be increased up to 75 mg or more per day in increments of 10-20 mg every 2 to 3 days.

2) Switching to zuclopenthixol decanoate:
In conjunction with the last injection of zuclopenthixol acetate (100 mg), an intramuscular injection of 200 mg–400 mg (1 ml–2 ml) of zuclopenthixol decanoate should be administered and repeated every 2 weeks. Higher doses and shorter intervals between injections may be necessary.
Zuclopenthixol acetate and zuclopenthixol decanoate can be mixed in a syringe for administration in a single injection.
Subsequent doses of zuclopenthixol decanoate and the intervals between injections will be determined based on the patient's response.

Elderly patients
: In elderly patients, it may be necessary to reduce the dose. The maximum dose of 100 mg is recommended.

Pediatric population:
The use of Clopixol Acutard in children is not recommended due to a lack of clinical data.

Renal insufficiency:
Clopixol Acutard can be administered to patients with renal insufficiency at the usual dosage.

Hepatic impairment:
Patients with hepatic impairment receive half the recommended dose and, if possible, blood level monitoring is advised.

Method of administration:
Clopixol Acutard is administered intramuscularly into the upper lateral quadrant of the gluteus maximus. Injection volumes exceeding 2 ml should be divided between two injection sites.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Circulatory collapse, decreased consciousness regardless of the cause (e.g. due to alcohol, barbiturate or opiate intoxication), coma.

4.4 Special warnings and precautions for use

As with any neuroleptic, there is a risk of developing neuroleptic malignant syndrome, the symptoms of which include hyperthermia, rigidity, unstable consciousness, and unstable autonomic nervous system function. However, the risk is higher with more potent neuroleptics. Patients with pre-existing cerebral insufficiency, intellectual disability, and a history of opiate and alcohol abuse are overrepresented among fatal cases.
Treatment involves discontinuing the neuroleptic and providing symptomatic support through general supportive measures. Administration of dantrolene and bromocriptine may be helpful.
Symptoms may persist for more than a week after discontinuation of oral neuroleptics, and sometimes even longer with depot formulations.

Extrapyramidal effects may occur, particularly during the first few days after injection and at the start of treatment. In most cases, these adverse effects can be satisfactorily controlled by reducing the dosage and/or administering antiparkinsonian drugs. The use of antiparkinsonian drugs is not recommended for routine prophylaxis. Antiparkinsonian drugs do not alleviate tardive dyskinesia and may worsen it. It is recommended to reduce the dosage or, when possible, discontinue treatment with zuclopenthixol. In cases of persistent akathisia, a benzodiazepine or propranolol may be helpful.

Dysphagia can occur secondary to extrapyramidal symptoms, as well as sialorrhea, sedation, or neuroleptic malignant syndrome, and can lead to life-threatening complications such as aspiration pneumonia and suffocation.

Like any other neuroleptic, zuclopenthixol acetate should be used with caution in patients with cerebral insufficiency, seizures, diabetes, or pronounced liver or kidney disease.

As has been described for other psychotropic drugs, zuclopenthixol acetate can alter blood levels of insulin and glucose; consequently, antidiabetic therapy should be adjusted in diabetics.

In cases of prolonged treatment, especially at high doses, close monitoring and periodic evaluation of the patient is recommended, with a view to reducing the maintenance dose.

Great caution is also necessary in patients suffering from angle-closure glaucoma or benign prostatic hyperplasia (BPH).

Hyperprolactinemia induced by taking Clopixol Acutard can negatively affect the prognosis of pre-existing breast cancer. Therefore, the drug should be administered with caution in such circumstances.

As with other drugs in the antipsychotic class, zuclopenthixol acetate can cause QT interval prolongation. Prolonged QT interval prolongation may increase the risk of malignant arrhythmias. For this reason, zuclopenthixol acetate should be used with caution in individuals at risk (hypokalemia, hypomagnesemia, or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g., QT prolongation, significant bradycardia (< 50 beats/min), recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmias.
Concomitant treatment with other antipsychotics should be avoided. (see section 4.5)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medications. Since patients treated with antipsychotics often have acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Clopixol Acutard, and preventive measures should be taken.

elderly patients

Cerebrovascular:
In randomized, placebo-controlled clinical trials with certain atypical antipsychotics, approximately three times the risk of cerebrovascular adverse events was observed in patients with dementia. The mechanism for this increased risk is unknown. A high risk cannot be excluded for other antipsychotics or for other patient groups. Zuclopenixol acetate should be used with caution in patients who have risk factors for a cerebrovascular event.

Increased Mortality in Older Adults with Dementia:
Data from two large-scale observational studies have shown that older adults with dementia who are treated with antipsychotics have a slightly increased risk of death compared to those who are not treated. There is insufficient data to provide a definitive estimate of the precise magnitude of the risk, and the cause of the increased risk is unknown.

Clopixol Acutard is not authorized for the treatment of behavioral disorders related to dementia.

4.5 Interactions with other medicinal products and other forms of interaction

Combinations requiring precautions for use:
Zuclopenthixol acetate may accentuate the sedative effect of alcohol, barbiturates and other drugs that cause central nervous system depression.

Neuroleptics can enhance or counteract the hypotensive effect of antihypertensives; the antihypertensive effect of guanfacine and similarly acting substances is counteracted.

Simultaneous use with lithium increases the risk of neurotoxic effects.

Neuroleptics lower the seizure threshold; therefore, caution is required when used concomitantly with other drugs that could cause seizures, e.g. tramadol.

Tricyclic antidepressants and neuroleptics can mutually inhibit their metabolism.

Zuclopenthixol acetate may decrease the effect of levodopa and adrenergic drugs.

Combining zuclopenthixol acetate with metoclopramide or piperazine may increase the risk of extrapyramidal symptoms.

Since zuclopenthixol is partially metabolized by CYP2D6, the concomitant use of drugs that inhibit this enzyme may decrease the plasma clearance of zuclopenthixol.

Regarding antipsychotic treatment, QT interval prolongation may be exacerbated by the concomitant administration of other drugs known to significantly prolong the QT interval. Concomitant administration of these drugs should be avoided.
The classes of drugs concerned include, but are not limited to:

- Class Ia and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol, dofetilide)
- Some antipsychotics (e.g., thioridazide)
- Some macrolides (e.g., erythromycin)
- Some antihistamines (e.g., terfenadine, astemizole)
- Some antibiotics in the quinolone group (e.g., gatifloxacin, moxifloxacin)

This list is not exhaustive and other specific drugs that are known to significantly prolong the QT interval (e.g. cisapride, lithium) should be avoided.

Zuclopenthixol acetate should be used with caution with drugs known to disrupt fluid/electrolyte balance, such as thiazide diuretics (hypokalemia), or known to increase plasma concentrations of zuclopenthixol acetate, as this may increase the risk of QT prolongation and malignant arrhythmias. (see section 4.4)

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
Zuclopenthixol acetate will only be used during pregnancy if the therapeutic benefit outweighs the fetal risk.

Newborns exposed to antipsychotics (including Clopixol Acutard) during the third trimester of pregnancy are at risk of adverse effects, including extrapyramidal effects and/or withdrawal symptoms after delivery, which can vary in severity and duration. The following effects have been reported: agitation, hypertonia, hypotonia, tremors, drowsiness, respiratory problems, or feeding difficulties. Therefore, newborns should be closely monitored.

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

Breastfeeding:
Given the low concentrations of zuclopenthixol found in breast milk, it is unlikely that a therapeutic dose would have any effect on the infant. The dose ingested by the newborn is less than 1% of the mother's daily dose per unit of weight (mg/kg). When the clinical benefit outweighs the risks, breastfeeding can be continued during treatment with zuclopenthixol acetate, but monitoring of the newborn, especially during the first 4 weeks after birth, is advised.

Fertility:
Side effects such as hyperprolactinemia, galactorrhea, amenorrhea, erectile dysfunction, and ejaculation disorders have been reported (see section 4.8). These side effects may negatively impact sexual function and fertility in women and/or men.

In the event of clinically significant hyperprolactinemia, galactorrhea, amenorrhea, or sexual dysfunction, a dose reduction (if possible) or discontinuation of treatment should be considered. Side effects are reversible upon discontinuation of treatment.

Animal studies have shown an adverse effect on fertility (see section 5.3).

4.7 Effects on the ability to drive vehicles and use machinery

Clopixol Acutard has a sedative effect. Patients taking this psychotropic medication may experience mild problems with attention and concentration. For this reason, caution is advised when driving or operating machinery.

4.8 Side effects

Most side effects are dose-dependent. The frequency and intensity of side effects most often occur during the initial phase of treatment and subside during the course of treatment.

The reported frequencies were taken from the literature and also from spontaneous reports. Frequencies are defined as follows:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Organ system classes	Frequency	Preferred term
Hematological and lymphatic system disorders	Rare	Thrombocytopenia, neutropenia, leukopenia, agranulocytosis
Immune system disorders	Rare	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Rare	Hyperprolactinemia
Metabolism and nutrition disorders	Frequent	Increased appetite, weight gain
	Uncommon	Decreased appetite, weight loss
	Rare	Hyperglycemia, impaired glucose tolerance, hyperlipidemia
Psychiatric disorders	Frequent	Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, decreased libido,
	Uncommon	Apathy, nightmares, increased libido, confusion
Disorders of the nervous system	Very common	Drowsiness, akathisia, hyperkinesia, hypokinesia, extrapyramidal symptoms (see section 4.4)
	Frequent	Tremors, dystonia, hypertonia, dizziness, headache, paresthesia, difficulty concentrating, amnesia, gait disturbances
	Uncommon to Rare	Tardive dyskinesia, hyperreflexia, dyskinesia, parkinsonism, syncope, ataxia, speech disorder, hypotonia, seizures, migraine
	Very rare	Neuroleptic malignant syndrome
Eye conditions	Frequent	Accommodation disorder, visual disturbances
	Uncommon	Oculogyric crisis, mydriasis
Ear and labyrinth disorders	Frequent	Vertigo
	Uncommon	Hyperacusis, ringing in the ears
Heart conditions	Frequent	Tachycardia, palpitations
	Rare	Electrocardiogram: QT interval prolongation
Vascular disorders	Frequent	Hypotension, orthostatic hypotension

	Uncommon	Hot flashes
	Very rare	Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, dyspnea
Gastrointestinal disorders	Very common	Dry mouth
	Frequent	Hypersalivation, constipation, vomiting, dyspepsia, diarrhea
	Uncommon	Abdominal pain, nausea, flatulence
	Rare	Dysphagia* (see section 4.4)
Hepatobiliary disorders	Uncommon	Abnormal liver function tests
	Very rare	Cholestatic hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, itching
	Uncommon	Rash, photosensitivity reaction, pigmentation disorder, seborrhea, dermatitis, purpura
Musculoskeletal and systemic disorders	Frequent	Myalgia
	Uncommon	Muscle rigidity, trismus, torticollis
Kidney and urinary tract disorders	Frequent	Urinary problems, urinary retention, polyuria
Pregnancy, puerperal and perinatal conditions	Frequency not known	Neonatal withdrawal syndrome (see section 4.6)
Diseases of the reproductive organs and breast	Uncommon	Ejaculation disorder, erectile dysfunction, female orgasmic disorder, vulvovaginal dryness
	Rare	Gynecomastia, galactorrhea, amenorrhea, priapism
General disorders and administration site abnormalities	Frequent	Asthenia, fatigue, malaise, pain
	Uncommon	Thirst, injection site reaction, hypothermia, fever

Dysphagia *can occur following extrapyramidal symptoms, as well as sialorrhea, sedation or neuroleptic malignant syndrome and can lead to life-threatening complications such as aspiration pneumonia and suffocation.*

As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, torsades de pointes and sudden death have been reported with 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, diarrhea, rhinorrhea, sweating, myalgia, paresthesia, insomnia, restlessness, anxiety, and agitation. Patients may also experience dizziness, alternating hot and cold flashes, and tremors. Generally, symptoms appear on days 1 to 4 after stopping treatment and subside after 7 to 14 days.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals should report any suspected adverse reactions via the national reporting systems:
in Belgium:
Federal Agency for Medicines and Health Products
www.afmps.be
Vigilance Division:
Website: www.notifieruneffetindesirable.be
Email: adr@fagg-afmps.be

In Luxembourg:
Regional Pharmacovigilance Centre of Nancy or Pharmacy and Medicines Division of the Directorate of Health.
Website: www.guichet.lu/pharmacovigilance

4.9 Overdose

Given the method of administration, symptoms of overdose are unlikely to occur.

Symptoms:
Drowsiness, coma, movement disorders, seizures, shock, hyper- or hypothermia.

In cases of overdose with medications known to affect the heart, ECG changes, QT interval prolongation, Torsades de Pointes, cardiac arrest, and ventricular arrhythmias have been observed.

Treatment
will be symptomatic and supportive. Measures should be taken to support the respiratory and cardiovascular systems. Epinephrine (adrenaline) will not be used, as it may exacerbate a drop in blood pressure. Seizures may be treated with diazepam, and extrapyramidal symptoms with biperiden.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: antipsychotic – thioxanthene derivative, ATC code: N05AF05.

Mechanism of action:
Zuclopenthixol is a neuroleptic belonging to the thioxanthene group.
The antipsychotic effect of neuroleptics is linked to their antagonistic effect on dopaminergic receptors, but blockade of the 5-HT (5-hydroxytryptamine) receptor likely also plays a role. *In vitro* , zuclopenthixol has a high affinity for both D1 and D2 dopaminergic receptors , as well as for α1 - adrenergic and 5-HT2 receptors , but no affinity for muscarinic cholinergic receptors. It possesses only weak antihistamine properties and does not block □2 - adrenergic receptors .

In vivo, affinity for D2 binding sites dominates over affinity for D1 receptors . Zuclopenthixol has demonstrated potent neuroleptic activity in all behavioral studies (dopamine receptor blockade). A correlation was found between *in vivo* test models , affinity for dopamine D2 binding sites in *vitro* , and average daily oral doses of the antipsychotic.

Like most neuroleptics, zuclopenthixol increases plasma prolactin levels.

Pharmacological studies have demonstrated a pronounced effect 4 hours after parenteral injection of zuclopenthixol acetate oily solution. A slightly more pronounced effect was observed after a period of one to three days following the injection. Efficacy decreased considerably in the days that followed.

Clinical efficacy and safety
In clinical use, zuclopenthixol acetate is intended for the initial treatment of patients with acute psychoses, mania and exacerbation of chronic psychoses.

A single injection of zuclopenthixol acetate rapidly produces a significant reduction in psychotic symptoms. This effect lasts for 2 to 3 days, and generally, one or two injections are sufficient for the patient to transition to treatment with the oral or depot formulation.

In addition to producing a significant reduction, or even a complete elimination, of the main symptoms of schizophrenia, such as hallucinations, delusions and thought disorders, zuclopenthixol also has a pronounced effect on accompanying symptoms, such as hostility, mistrust, agitation and aggression.

With zuclopenthixol, some dose-dependent but transient sedation can be expected. However, in the acute phase of the illness, such initial sedation is usually considered an advantage, as the patient calms down during the acute phase before the antipsychotic effect takes hold.
This nonspecific sedative effect appears rapidly after injection, becomes significant after 2 hours, and reaches its maximum within 8 hours, after which it diminishes substantially and remains weak despite repeated injections.

Zuclopenthixol acetate is especially useful for treating psychotic patients who are agitated, disturbed, hostile, or aggressive.

5.2 Pharmacokinetic properties

Absorption:
Esterification of zuclopenthixol by acetic acid yields a more lipophilic substance: zuclopenthixol acetate. Solubilized in fluid vegetable oil and injected intramuscularly, this substance diffuses slowly into the interstitial fluid, where it undergoes enzymatic hydrolysis, releasing the active ingredient: zuclopenthixol.

The maximum serum concentration is reached within 24–48 hours (average 36 hours) after intramuscular injection. The mean serum elimination half-life (which reflects the release of the oily phase) is approximately 32 hours.

Distribution
The apparent volume of distribution (Vd) β is ± 20 l/kg.
Binding to serum proteins is approximately 98–99%.

Biotransformation:
Zuclopenthixol is metabolized via three main pathways: sulfoxidation, N-dealkylation of the side chain, and glucuronidation. The metabolites have no psychopharmacological activity. In the brain and other tissues, the concentration of zuclopenthixol is higher than that of its metabolites.

Elimination:
The elimination half-life (T _{1/2β}) of zuclopenthixol is approximately 20 hours and the mean blood clearance (CL _s) is approximately 0.86 L/min.
Zuclopenthixol is primarily excreted in the feces and to a lesser extent (10%) in the urine.

Only about 0.1% of the dose is excreted unchanged in the urine, indicating that the influence of the drug on the kidneys is negligible.

Zuclopenthixol is secreted in small amounts into breast milk in breastfeeding mothers. The steady-state milk/serum concentration ratio was approximately 0.29 after oral administration (or administration of the depot form) in women.

Linearity/Non-linearity:
The kinetics are linear. The mean peak plasma concentration corresponding to 100 mg of zuclopenthixol acetate is 102 nmol/L (41 ng/mL). Three days after injection, the serum concentration is approximately 1/3 of the peak concentration, i.e., 35 nmol/L (14 ng/mL).

Elderly patients:
Pharmacokinetic parameters are largely independent of patient age.

Decreased renal function
Based on the elimination characteristics described above, it can be reasonably estimated that a decrease in renal function should not significantly influence plasma levels of the parent substance.

Decreased liver function:
No data available

Polymorphism
An *in vivo* study showed that metabolism is partly subject to genetic polymorphism of sparteine/debrisoquine oxidation (CYP2D6).

5.3 Preclinical safety data

Chronic toxicity:
In chronic toxicity studies, there were no worrying results regarding the therapeutic use of zuclopenthixol.

Reproductive toxicity:
In a three-generation rat study, delayed mating was observed. After mating, there was no effect on fertility. In a study where zuclopenthixol was administered via food, impaired mating ability and a decreased chance of conception were observed.

Animal reproduction studies have shown no embryotoxic or teratogenic effects. In peri- or postnatal studies in rats, doses of 5 and 15 mg/kg/day resulted in increased stillbirths, decreased pups survival, and delayed development in offspring. The relevance of these findings is unclear, and it is possible that the effect on the pups was due to neglect by the dam, who was exposed to toxic doses during gestation.

Mutagenicity and Carcinogenicity:
Zuclopenthixol has neither mutagenic nor carcinogenic potential.
An oncogenicity study in rats at a dose of 30 mg/kg/day (the highest dose) for 2 years resulted in a small increase in the incidence of mammary adenocarcinoma of the pancreatic islets, carcinomas in females, and parafollicular thyroid carcinomas; these results are not statistically proven. The small increase in the incidence of these tumors is the general result for D2 antagonists that increase prolactin secretion when administered to rats. Physiological differences between rats and humans with respect to prolactin make the clinical relevance of these results unclear; however, it is presumed that this is not a predictor of oncogenic risk for the patient.

Local toxicity:
Local muscle damage has been observed after injection of neuroleptics solubilized in aqueous solutions, including zuclopenthixol. Muscle damage is progressively greater with aqueous solutions of neuroleptics than with oily solutions of zuclopenthixol acetate and zuclopenthixol decanoate.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Medium-chain saturated triglycerides

6.2 Incompatibilities

Zuclopenthixol acetate can only be mixed with zuclopenthixol decanoate for which the solvent is also medium-chain saturated triglycerides (Pharm eur.).

Zuclopenthixol cannot be mixed with other depot preparations that contain sesame oil, as this can permanently alter the pharmacokinetic properties of the preparations concerned.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep the ampoules in the outer packaging, away from light.

6.5 Nature and contents of the outer packaging

Colorless ampoules (type I glass) of 1 ml.
Cardboard boxes containing 1 x 1 ml, 5 x 1 ml.

Not all presentations may be commercially available.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Lundbeck sa
Stephanie Square Centre
Avenue Louise 65/11
1050 Brussels

8. MARKETING AUTHORISATION NUMBER

BE140987
LU: 2005088296

- 0165997: CLOPIXOL-ACUTARD SOL.INJ. 50 MG/I MLI*I AMP. 1ML
- 0195724: CLOPIXOL-ACUTARD SOL.INJ. 50MG/1ML1*5AMP. 1ML

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of initial authorization: April 11, 1988
Date of last renewal: January 28, 2005

10. TEXT UPDATE DATE

Date of text approval: 01/2026
Date of text update: 01/2026