1. NAME OF THE MEDICINAL PRODUCTS

FLUDECATE Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of Fludecate contains 25 mg/ml of fluphenazine decanoate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intramuscular injection
Yellow, oily viscous, clear solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fludecate is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral neuroleptic therapy (e.g. chronic schizophrenics).

Fluphenazine Decanoate Injection has not been shown effective in the management of behavioral complications in patients with mental retardation.

4.2 Posology and method of administration

Posology

The response to fluphenazine decanoate differs from patient to patient. The dosage, duration of use and intervals between injections for relapse prevention must be adjusted to the individual response, the indication and the severity of the disease. For this, the principle of having as low a dose and as short a duration of treatment as possible should be followed.

In general, 12.5-100 mg fluphenazine decanoate is injected at intervals of 3 (2-4) weeks after the conclusion of antipsychotic treatment with short-acting neuroleptics. If treatment is continued with oral neuroleptics (and other medicinal products, see section 4.5), a sufficient safety margin needs to be allowed for, given that Fludecate acts for 2-4 weeks.

The maximum single dose should not exceed 100 mg. If doses above 50 mg are necessary, the dose should be cautiously increased in 12.5 mg steps up to the target dose.

Once remission has occurred - especially with accompanying stabilizing socio- and psychotherapeutic measures - lower doses (12.5-25 mg fluphenazine decanoate every 3 (2-4)

weeks) are frequently sufficient for relapse prevention. However, doses of 2.5 mg fluphenazine decanoate every 2 weeks or 50 mg every 2 weeks may also be necessary.

If very low doses are used, it may be necessary to switch to suitable strengths.
The stated dosages refer to adult patients with a stable circulation. The onset of action of a single dose occurs between day 2 and 5 after administration, and in chronic courses often later.

Note

Fludecate are oily solutions for injection. Intra-arterial and intravenous injections must be avoided, as there is the danger of necrosis. Paravenous injection causes severe pain.

Children and adolescents

Fludecate is contraindicated in children under the age of 12 (see section 4.3).

In children over 12 years of age and adolescents, Fludecate should only be prescribed after careful assessment of the benefit-risk ratio because of insufficient data on safety and efficacy (see section 4.4).

Special dosage instructions

Fludecate should not be used for initial treatment or for elderly or frail patients or other patients at increased risk of adverse reactions (e.g., patients with hepatic or renal impairment, organic brain disorders, circulatory or respiratory failure).
Fludecate should be carefully dosed in patients with glaucoma, urinary retention and prostatic hyperplasia, given its anticholinergic effects.

Method and duration of administration

Fludecate must be given by slow, deep intramuscular injection (caution is needed in the presence of thrombolytic therapy), using a dry needle and syringe to avoid turbidity of the solution.
The dosing interval is at least 2 weeks, and on average 3 (2-4) weeks.

In patients in remission, the effect may last for up to 6 weeks in individual cases.

The length of treatment depends on the clinical features and individual course. The lowest necessary maintenance dose should be aimed for. The need for continued treatment should be critically assessed on an ongoing basis.
After longer-term therapy, an injection dose of more than 25 mg fluphenazine decanoate must be reduced in very small steps over a long period of time and with close contact between the doctor and patient.

4.3 Contraindications

- Hypersensitivity to the active substance, neuroleptics (especially phenothiazines), sesame oil or to any of the excipients listed in section 6.1.
- Pre-existing prolactin-dependent tumors: pituitary prolactinomas and breast cancer.
- Acute intoxication with central depressants (e.g., opiates, hypnotics, antidepressants, neuroleptics, tranquillizers) or alcohol.
- Severe blood cell or bone marrow injury.
- Leukopenia and other hematopoietic disorders.
- Parkinson’s disease.
- Known history of neuroleptic malignant syndrome after fluphenazine.
- Severe hepatic disorders.
- Severe depression.

- Coma.
- Children under 12 years

4.4 Special warnings and precautions for use

Fludecate must be used only after a rigorous benefit-risk assessment and with special caution in

- Hepatic and renal impairment.
- Pheochromocytoma.
- Hypotension, Hypertension, Orthostatic Dysregulation, Bradycardia, Hypokalemia.
- Congenital long QT syndrome or family history of QT syndrome or other clinically significant cardiac disorders (especially coronary heart disease, conduction disorders, arrhythmias).
- Concomitant treatment with medicinal products that also prolong the QT interval on the ECG or that can cause hypokalemia or other electrolyte disturbances (see section 4.5).
- History of organic brain disorders and epileptic seizures.
- Suspected or neurologically recognizable subcortical brain injury.
- Depressive disorder.
- Chronic respiratory conditions and asthma.
- Severe quantitative impairment of consciousness, e.g., somnolence.
- Glaucoma, pyloric stenosis, prostatic hyperplasia, urinary retention.
- Patients exposed to high temperatures.
- Use of organophosphate insecticides.
- Concomitant treatment with other neuroleptics should be avoided (see section 4.5).

Children and adolescents

There are insufficient studies on the efficacy and tolerability of fluphenazine in children and adolescents. Fludecate should therefore only be prescribed in children over the age of 12 and adolescents after careful assessment of the benefit-risk ratio.

Tardive dyskinesia

Although the prevalence of tardive dyskinesia has not yet been sufficiently researched, it appears that elderly patients, in particular elderly women, are particularly predisposed to it. The risk of tardive dyskinesia, and especially the risk of irreversibility, presumably increases with the length of treatment and level of the neuroleptic dose. However, tardive dyskinesia can also occur even after a short period of treatment and using low doses. Neuroleptic treatment itself can initially mask the symptoms of incipient tardive dyskinesia. After discontinuation of the medication, the tardive dyskinesia then becomes obvious. There is currently no established therapy for these symptoms.

Increased mortality in elderly patients with dementia disorders

The data from two large observational studies showed that elderly patients with dementia disorders treated with conventional (typical) antipsychotics have a slightly increased risk of mortality compared with those not treated with antipsychotics. The available study data do not allow the exact extent of this risk to be stated and the reason for the increased risk is not known.

Fluphenazine decanoate is **not indicated** for the treatment of behavioral disorders associated with dementia disorders.

Increased risk of adverse cerebrovascular events

In randomized, placebo-controlled clinical studies in patients with dementia who were treated with some atypical antipsychotics, there was noted to be an approximately three-fold increased risk of adverse cerebrovascular events. The mechanism leading to this increase in

risk is not known. It is not possible to rule out this effect also occurring with the use of other antipsychotics or in other patient groups. Fluphenazine decanoate should therefore be used with caution in patients at increased risk of stroke.

Risk of thromboembolism
Cases of venous thromboembolism (VTE) have been reported in association with the use of antipsychotics. As patients treated with antipsychotics frequently have acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with fluphenazine decanoate and preventive measures taken.

Special caution is required in patients with organic brain damage arteriosclerotic cerebrovascular disorders, and a tendency to seizures (in the medical history, e.g., in the context of alcohol withdrawal) as fluphenazine lowers the seizure threshold. The occurrence of seizures is more likely, especially with high doses in the begining of treatment, rapid increase in doses and abrupt discontinuation of high doses. Patients with epilepsy should be treated with Fludecate only if anticonvulsant therapy is being used concomitantly.

In disorders of the basal ganglia, Fludecateshould only be used in exceptional cases and the treatment should be stopped if symptoms worsen. In patients with depression, Fludecate should only be used in conjunction with an antidepressant as Fludecate can worsen symptoms of depression. Fludecate must not be used in severe depressive disorders (see section 4.5).
Patients with pheochromocytoma, renal failure, heart failure or cerebral insufficiency develop more frequently hypotensive reactions due to fluphenazine administration and should therefore be carefully monitored.
Neuroleptics result in increased prolactin secretion. Experiments in tissue cultures *in vitro* suggest that approximately a third of breast tumors are prolactin-dependent. Although there are not yet any informative clinical or epidemiological studies available, caution is advised if there is a relevant history.
The blood count (including differential and platelet count) should be checked prior to treatment with Fludecate Treatment with Fludecate must not take place if the blood counts are abnormal (see sections 4.3 and 4.8).
After intitating treatment the blood count (including differential count) should be checked weekly for a period of four months. If the results obtained are normal, the interval between checks can then be lengthened. If the white cell count falls rapidly, especially to values below 3000/mm^3, or if other blood count abnormalities occur, treatment with tricyclic neuroleptics should be stopped immediately and replaced by other forms of treatment. Intensive care measures should be implemented if necessary. The blood count must be monitored until it has returned to normal.
The patient should be instructed not to self-medicate with analgesics/antibiotics if he/she develops ahigh temperature, inflammation of the gums or oral mucosa, sore throat, purulent tonsillitis or flu-like symptoms, especially if these symptoms occur within the first three months after starting treatment with the drug, but instead to consult his/her attendant physician immediately.
Body weight, blood glucose and serum lipid levels, and dental status should be monitored at regular intervals.
Renal and hepatic function should be monitored at regular intervals during therapy.
Conduction disorders may occur, especially in elderly patients and patients with pre-existing heart damage. The circulatory status (including an ECG recording) should be monitored at regular intervals during therapy, and a baseline ECG should be available for subsequent monitoring of any changes.

Pre-existing hypokalemia should be corrected before initiate treatment.

The possibility of the occurrence of neuroleptic malignant syndrome (high body temperature, muscle rigidity, impaired consciousness, autonomic nervous system instability) exists with all neuroleptics. The symptoms are often misdiagnosed as catatonia. As further administration of a neuroleptic can be life-threatening in this situation, the differential diagnosis is extremely important (including medication history, examination for muscle rigidity, high body temperatureand elevation of blood creatine kinase activity, elevation of myoglobin in the blood and urine). Cases with a fatal outcome are particularly prevalent among patients with a pre-existing organic brain syndrome, intellectual impairment and opiate or alcohol dependence. The symptoms may persist in a dose-dependent manner (corresponding to the treatment intervals) for a considerable time after the IM injection (forundesirable effects, see section 4.8).

The doses must be adjusted in hepatic or renal impairment. Special caution is required, especially in elderly patients, because of increased sensitivity. The anticholinergic adverse reactions are frequently more pronounced. Elderly patients may develop extrapyramidal adverse reactions, even at low doses. The frequency of tardive dyskinesia is increased . The sedative effect is alsomore pronounced in elderly patients. Hypotension may occur more frequently among elderly.

Excipients of Fludecate

Fludecate contains 15 mg benzyl alcohol, which may cause allergic reactions. Fludecate must be used with caution in patients with renal or hepatic impairment, or in patients who are pregnant or breast feeding, because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

When other central depressant medicinal products (hypnotics/sedatives, analgesics, other psychiatric drugs, antihistamines), anesthetics or alcohol are used concomitantly, there may be reciprocal potentiation of the effects and adverse reactions (especially sedation and blood pressure lowering).
If patients on high neuroleptic doses undergo surgery, it is essential to carefully monitor for hypotension. The dose of the anesthetic or central depressant substances should be reduced in certain circumstances.
The concomitant administration of tricyclic antidepressants and fluphenazine leads to a rise in plasma antidepressant levels, and increased toxicity of both active substances (anticholinergic effect, lowering of seizure threshold, but above all cardiac effects [QT-interval prolongation]) needs to be anticipated. For this reason, this combination is not recommended.
The concomitant use of medicinal products that can also prolong the QT interval (e.g., class IA or III antiarrhythmics, macrolide antibiotics, antimalarials, antidepressants, other neuroleptics, antihistamines), result in hypokalemia or other electrolyte disturbances (e.g., certain diuretics) .or inhibit CYP2D6-mediated hepatic metabolism of fluphenazine (e.g., paroxetine, fluoxetine) should be avoided.
Combination with lithium salts can increase plasma fluphenazine levels. This increases the risk of extrapyramidal motor adverse reactions (gait disorders, hyperkinesia of the proximal parts of the body, tremor, rigidity, in isolated cases, brain damage that is difficult to reverse).

Conversely, the lithium plasma levels may also be increased. Severe neurotoxic syndromes have been reported very rarely with concomitant administration of neuroleptics and lithium.
When treatment with levodopa or dopamine agonists (e.g., bromocriptine, amantadine, cabergoline) is being given concomitantly, their effect may be attenuated.
With combined use of neuroleptics and other dopamine antagonists (e.g., metoclopramide, alizapride), the extrapyramidal motor effects may be more pronounced.
When fluphenazine is combined with medicinal products that also have an anticholinergic effect (e.g., antidepressants, atropine, biperiden), the anticholinergic effects may be additively increased. This can manifest as visual disturbances, an increase in intraocular pressure, dry mouth, an accelerated heart rate, constipation, problems with micturition, disorders of saliva secretion, speech block or memory disorders; the risk of drug-induced delirium is increased. The effect of fluphenazine may be simultaneously attenuated.
Combinations with sympathomimetics can result in hypertensive crises.
In patients on fluphenazine, hypotension should not be treated with epinephrine as epinephrine administration can lead to a further fall in blood pressure ("reverse epinephrine effect"). Norepinephrine (noradrenaline) may, however, be administered in severe shock states (see section 4.9).
Fluphenazine decanoate generally increases the hypotensive effect of antihypertensive drugs. This may give rise to the increased occurrence of orthostatic circulatory dysregulation. However, paradoxical reactions have also been described (guanethidine, clonidine, methyldopa).
The concomitant administration of monoamine oxidase (MAO) inhibitors can lead to a (further) fall in blood pressure and extrapyramidal motor effects.

The concomitant use of reserpine-containing products is not advised.

Respiratory depression caused by polypeptide antibiotics (e.g., colistin, polymyxin B) can be exacerbated by fluphenazine.

The effect of anticoagulants may be increased. For this reason, regular monitoring of the coagulation status is indicated at shorter intervals if anticoagulant therapy is being undertaken simultaneously.

The concomitant use of anticonvulsants, such as barbiturates or carbamazepine, can result in increased metabolism of fluphenazine.

The concomitant use of fluphenazine and phenytoin can lead to an alteration of phenytoin metabolism. This can give rise to toxic plasma levels in some circumstances.

Due to the fluphenazine-induced increase in prolactin, the response to gonadorelin administration may be reduced.

Fluphenazine decanoate should not be combined with clozapine as the risk of a blood disorder is potentially increased.

When fluphenazine decanoate and propranolol are used simultaneously, the plasma levels of both medicines are increased.

Concomitant treatment with piperazine-containing anthelmintics leads to an increased risk of extrapyramidal motor adverse reactions.

Clonidine can decrease the antipsychotic effect of fluphenazine.

When fluphenazine and cimetidine are used concomitantly, the plasma level of fluphenazine may be decreased.

Concomitant use of pentetrazol can trigger cerebral seizures.

Phenothiazines can increase the tendency to metrizamide-induced seizures. Fluphenazine should therefore not be given for at least 48 hours before and 24 hours after a myelogram.

The concomitant administration of fluphenazine with amphetamines or anorectics can result for antagonistic pharmacological reactions.

In individual cases, acute, severe, reversible parkinsonism have been reported by patients on combination therapy with a serotonin reuptake inhibitor and fluphenazine.

There is evidence that concomitant use of phenylalanine and neuroleptics increases the risk of the occurrence of tardive dyskinesia.

Patients receiving fluphenazine as treatment should avoid dehydroepiandrosterone replacement therapy as there have been cases reported where patients with elevated dehydroepiandrosterone levels did not respond to therapy with antipsychotics.

An increased risk of epileptic seizures has been described in schizophrenic patients who took products containing evening primrose oil while on treatment with phenothiazines.
Caffeine potentially counteracts the antipsychotic properties of phenothiazines. The data are, however, contradictory.

The metabolic control of insulin-requiring diabetics on phenothiazine treatment (especially with high doses) may become unstable and potentially require dietary and pharmacological measures or adjustment of antidiabetic therapy.

The result of a pregnancy test may be distorted (false-positive result) during treatment with fluphenazine decanoate.

Note

The patient should be told not to take any other medicinal products, including those obtained without a prescription, without the knowledge of the attendant physician.

4.6 Fertility, pregnancy and lactation

Pregnancy

To date, there is only clinical experience with the use of low oral doses (0.5 mg/day) in pregnant women. Fluphenazine showed reproductive toxicity in animal studies (see section 5.3). As the safety of use during pregnancy has not been demonstrated, fluphenazine decanoate should therefore only be prescribed during pregnancy if there is a compelling indication and after a very careful assessment of the therapeutic benefit for the mother versus the risks of harm to the fetus or child.

Phenothiazines can cross the placenta. In order to prevent reversible adverse reactions (extrapyramidal disorders, cholestatic jaundice, withdrawal symptoms, slight abnormalities of limb posture) in the newborn, it is recommended to use as low doses of neuroleptics as possible in the last weeks of pregnancy.

Newborns exposed to antipsychotics (including fluphenazine decanoate) during the third trimester of pregnancy are at risk of adverse reactions, including extrapyramidal symptoms and/or withdrawal symptoms, the severity and duration of which can vary after birth.

There have been reports of agitation, increased or decreased muscle tone, tremor, somnolence, dyspnea and feeding disorders. Accordingly, newborns should be carefully monitored.

Lactation

Fluphenazine is excreted in human milk. therefore Breast-feeding should not take place during treatment.

4.7 Effects on ability to drive and use machines

Even when used correctly, Fludecate can alter the ability to react to such an extent that the ability to drive or use machines is compromised. This applies even more so in conjunction with alcohol. Therefore patients should completely avoid driving vehicles, using machines or undertaking other dangerous activities, at least during the first phase of treatment. In each specific case, the decision is made by the attendant physician taking into account the individual response and relevant dosage.

4.8 Undesirable effects

The frequencies for adverse reactions are based on the following categories:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)
Adverse reactions due to fluphenazine decanoate are comparatively rare and mild in the lower dosage range. Some adverse reactions occur more frequently at higher doses. Neurological symptoms are the most common in this context.

Central nervous system

Extrapyramidal motor symptoms
Early dyskinesia can occur very frequently during treatment with fluphenazine, especially in the first days and weeks. Parkinsonism and akathisia generally occur somewhat later. Dystonia (torticollis, rigidity of the back muscles) and hyperreflexia are also possible. Children develop extrapyramidal motor disorders even at low doses.
If early dyskinesia or parkinsonism occurs, a dose reduction or treatment with an anticholinergic antiparkinsonian agent is necessary. However, this medication should only be used if required and not given routinely. If there is a need for antiparkinsonian medication that is excreted more rapidly than fluphenazine, it may be necessary to continue this antiparkinsonian medication even after fluphenazine has been discontinued in order to prevent the occurrence or worsening of extrapyramidal motor symptoms. The potential increase in intraocular pressure with the concomitant administration of fluphenazine and anticholinergic agents, including antiparkinsonian agents, needs to be borne in mind (see section 4.5).
It is difficult to treat akathisia; a dose reduction can initially be tried, and if this is unsuccessful, a trial of treatment with sedatives, hypnotics or beta-receptor blockers can be undertaken.
Tardive dyskinesia (persistent, in many cases irreversible hyperkinetic syndromes with abnormal involuntary movements primarily involving the jaw and facial muscles, but also athetoid and ballistic movements of the limbs) may occur, mostly after longer-term and high-dose therapy or after treatment discontinuation. There is currently no established therapy for these symptoms.
It is essential to watch for the first signs of dyskinesia, primarily in the region of the tongue and orofacial muscles, and to consider stopping the neuroleptic therapy.
Tardive dyskinesia may be masked during long-term treatment with Fludecate and observed only after the end of treatment (see section 4.4).

Neuroleptic malignant syndrome

A life-threatening neuroleptic malignant syndrome (temperature above 40°C, muscle rigidity, autonomic dysregulation with palpitations and hypertension, impaired consciousness and even coma, a rise in myoglobin and creatine kinase activity (CK)) can occur during neuroleptic treatment, requiring immediate discontinuation of the medication. The frequency of this syndrome is reported to be 0.07-2.2%.

Treatment is difficult and the following measures are recommended:

- No further administration of the medicine.
- Treatment of hyperthermia through cooling as antipyretics are potentially ineffective for a high body temperature,
- Treatment of electrolyte and fluid disturbances, cardiovascular manifestations, infections, and respiratory and renal complications,
- Therapy attempt with dantrolene infusions (3 to 10 mg/kg body weight/day) in combination with bromocriptine (7.5 to 30 mg/day orally).

Other CNS effects

Particularly at the beginning of treatment, tiredness and sedation can frequently occur, but restlessness, agitation, drowsiness, depression (especially during long-term therapy), lethargy, dizziness, headache, confused dreams, symptoms of delirium (especially during combination with anticholinergic substances), cerebral seizures, and dysregulation of body temperature (hyper- and hypothermia) are also possible as well as occasional speech, memory and sleep disorders. Isolated cases of reversible central paresis have been reported.
Changes in the EEG and cerebrospinal fluid protein may also occur during treatment withFludecate .
As occurs on other neuroleptics, psychotic processes may rarely be reactivated or exacerbated.

Cardiovascular system

Hypotension or orthostatic dysregulation and reflex acceleration of heart rate (circulatory instability) frequently occur, particularly at the beginning of treatment. ECG changes have been observed (disorders of conduction and repolarization), as well as hypertension. Fluphenazine can prolong the QT interval in the ECG; in some instances, life-threatening torsades de pointes and even ventricular fibrillation may occur (see sections 4.4 and 4.5). The treatment with fluphenazine should be stopped in these cases. Ventricular arrhythmias, ventricular tachycardia (rare), cardiac arrest and sudden unexplained death have been reported with medicinal products that are members of the therapeutic class of neuroleptics.
Ventricular arrhythmias may occur more frequently when high doses are administered and in predisposed patients.

Autonomic nervous system / gastrointestinal tract

Autonomic adverse reactions occur primarily at the beginning of treatment and then generally show adaptation.
Accommodation disorders, dry mouth, sweating, salivation, polyuria, high body temperature, the feeling of a blocked nose, nasal congestion, raised intraocular pressure, constipation (in some cases even paralytic ileus) and urinary retention can uncommonly occur.

Nausea, vomiting, diarrhea, loss of appetite and dyspepsia have also been uncommonly reported. These effects can usually be favorably impacted by a dose reduction or prolonged dosing interval.

Liver and bile ducts

Transient elevations of liver enzyme activities have been uncommonly reported; hepatitis (usually cholestatic) has also been very rarely reported. Jaundice can also occur.

Endocrine system

Fluphenazine decanoate can affect sexual functions (impaired sexual response, decreased libido, erectile and ejaculatory disorders); menstrual disorders, galactorrhea and gynecomastia can occur, as well as disorders of glucose metabolism.

Like other neuroleptics, fluphenazine decanoate can lead to an increase in body weight, impaired ADH secretion and hyponatremia.

Blood and blood vessels

Hematopoietic disorders in the form of leukopenia, thrombocytopenia, eosinophilia and pancytopenia have been reported uncommonly. agranulocytosis and leg and pelvic vein thrombosis have been rarely reported.
Not known (cannot be estimated from the available data):
Cases of thromboembolic disease (including cases of pulmonary embolism and cases of deep vein thrombosis).

Pregnancy, puerperium and perinatal conditions

Not known (cannot be estimated from the available data):

Drug withdrawal syndrome in the newborn (see section 4.6).

Skin and hypersensitivity reactions

Allergic skin reactions of all severities (e.g., pruritus, erythema, urticaria, eczema, exfoliative dermatitis) and photosensitivity can occur (caution is needed if exposed to sunlight).

Respiratory symptoms, asthma and bronchopneumonia, laryngeal edema, angioneurotic edema (Quincke's edema), anaphylactic reactions, pigmentation disorders, lupus-like syndromes and peripheral edema have been observed.

The following have also been described

Cerebral edema, retinitis pigmentosa, pigment deposits in the lens and cornea (see section 5.3).
In hospitalized psychotic patients, sudden, unexpected and unexplained deaths have occurred during phenothiazine therapy, with previous brain injury or seizures probably playing a role as predisposing factors; high doses should therefore be avoided in patients with known seizures.

Sesame oil can rarely cause severe allergic reactions.

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. 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

Additionally, you can report to Unipharm Ltd. via the following address:
https://unipharm.co.il/

4.9 Overdose

Intoxications generally occur only after more severe overdoses because of the relatively wide therapeutic range.

Symptoms of overdose

In the event of an overdose, the adverse reactions described in section 4.8, in particular, can occur with increased severity, depending on the dose administered:

- extrapyramidal disorders: acute dyskinetic or dystonic symptoms, glossopharyngeal dystonia. oculogyric crises, laryngeal or pharyngeal spasms.
- somnolence and even coma, occasionally agitation and confusion with delirium.
- cerebral seizures.
- hyperthermia or hypothermia.
- cardiovascular: hypotension, but also hypertension, tachycardia or bradycardia, ECG abnormalities such as arrhythmia (PQ or QT interval prolongation, torsades de pointes), heart and circulatory failure (rapid if massive intoxication),
- anticholinergic effects: blurred vision, raised intraocular pressure, glaucoma attack, reduced intestinal motility, urinary retention.
- respiratory complications: respiratory depression, respiratory arrest, aspiration, cyanosis, pneumonia.

Measures in the event of overdose

Intensive care treatment should be initiated as quickly as possible.

Treatment is symptomatic. Volume replacement, anticonvulsants and vasoconstrictors (norepinephrine, not epinephrine) may be used and, if there are cardiac complications, antiarrhythmics and/or sodium hydrogen carbonate or lactate may be necessary.
The ECG and vital signs should be monitored until the ECG has returned to normal. Analeptics are contraindicated as there is a tendency to cerebral seizures due to the lowering of the seizure threshold caused by fluphenazine decanoate. Beta-blockers should also be avoided because they increase vasodilatation.
If there are severe extrapyramidal symptoms, antiparkinsonians, e.g., biperiden, should be administered IV; in some cases, it may be necessary to administer the antiparkinsonian medication for several weeks.

Highbody temperature should be treated with antipyretics, and with ice baths if necessary. Hypothermia should be treated by slow warming.

If an anticholinergic syndrome occurs, physostigmine salicylate is available as an antidote for use under intensive care conditions (with ECG monitoring).

Given the large volume of distribution and high degree of plasma protein binding, forced diuresis and hemodialysis are not very useful in the case of pure fluphenazine intoxications.

Diazepam should only be given to treat seizures if facilities for artificial ventilation are available (because of the risk of respiratory depression).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics; phenothiazine with piperazine structure

ATC code: N05AB02

Mechanism of action

Fluphenazine decanoate is a highly potent neuroleptic of the phenothiazine class. It primarily causes blockade of dopamine receptors and thereby reduces the effect of dopamine as a transmitter substance. Fluphenazine has a high affinity for D2- receptors. An increase in prolactin, a decrease in apomorphine and amphetamine hyperactivity andcatalepsy occur as a result.

The muscarinic acetylcholine, D1 and H1 receptors, and α1 adrenergic receptors are blocked to a lesser extent by fluphenazine.

The clinical profile of action is characterized by antipsychotic effects: reduction of delusion, hallucinations, schizophrenic self-disorders and disordered thinking, suppression of psychomotor agitation and affective tension.

The extrapyramidal motor adverse reactions are explained by the inhibition of dopaminergic transmission in the corpus striatum.

5.2 Pharmacokinetic properties

Absorption

Following intramuscular injection of the oily solution, fluphenazine decanoate is broken down slowly to the non-esterified fluphenazine.

Distribution

Fluphenazine then reaches the bloodstream and from there enters the tissues and its site of action. This process occurs over a period of approximately 2-4 weeks after injection of fluphenazine decanoate and ensures therapeutically active levels for the interval between injections.

After administration of the depot preparation, a high blood level is reached within a few hours; this then rapidly falls again and on day 3 moves into a plateau phase with only a subsequent slight decrease.

Fluphenazine is distributed throughout the body because of its highly lipophilic nature. The volume of distribution is approximately 25 L/kg body weight. Fluphenazine is excreted in human milk and crosses the placenta and blood-brain barrier. Plasma protein binding is over 95%. The plasma half-life is approximately 20 hours.

Metabolism / elimination

Fluphenazine is almost completely broken down by the liver. In addition to glucuronidation of the hydroxyl group in the side chain, there is hydroxylation of the phenothiazine base via CYP2D6, sulfoxidation, dealkylation of the piperazine ring and subsequent cleavage of the ring. After glucuronidation, 80-95% of excretion is via bile.

5.3 Preclinical safety data

The symptoms of acute fluphenazine intoxication are described in section 4.9. Besides the known pharmacological effects, studies on chronic toxicity in rats did not show any evidence of toxic effects. Lens opacities have been observed in dogs in a long-term study. In *in vitro* studies, fluphenazine also showed marked phototoxicity with accumulation in the retinal epithelium. These findings are evidently associated with pigment deposits in the lens and cornea (idiosyncratic retinopathy) which have been observed in patients after long-term high-dose phenothiazine therapy.

All available *in vitro* and *in vivo* studies with fluphenazine decanoate suggest there is no significant evidence of a mutagenic potential.

There are no long-term animal studies on the carcinogenic potential of fluphenazine.

The reproductive toxicity of fluphenazine has only been studied in non-conventional studies. In these, fluphenazine had a negative effect on male rat fertility. In an embryotoxicity study, fluphenazine led to organ malformations in mice. Embryotoxicity studies in rats showed contradictory findings regarding teratogenic effects. The period of gestation was prolonged on fluphenazine. Effects on the behavior of the progeny were not studied.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sesame oil and Benzyl alcohol

6.2 Incompatibilities

Fludecate must not be mixed with other injection or infusion solutions.

6.3 Shelf life

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

6.4 Special precautions for storage

Store bellow 25°C.

Protect from light.

6.5 Nature and contents of container

Fludecate ampoules:

Amber glass type I ampoules

Original pack 1 ml of solution ampoule packed in a carton packs.

Each pack contains 5 ampoules

6.6 Special precautions for disposal and other handling

No special requirements.

7. LICENSE HOLDER AND IMPORTER

Unipharm Trading Ltd., POB 21429, Tel-Aviv 6121301

8. MARKETING AUTHORIZATION NUMBERS

025 22 21358 00

9. DATE OF REVISION OF THE TEXT

Revised in June 2022 according to MOHs guidelines