PRODUCT MONOGRAPH

[Pr]Flupentixol Decanoate Injection BP

Flupentixol Injection BP

Flupentixol Decanoate BP, 20 mg/mL and 100 mg/mL

Sterile

Antipsychotic

Sandoz Canada Inc.
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ACTION AND CLINICAL PHARMACOLOGY

Flupentixol decanoate is the decanoate ester of a thioxanthene derivative with antipsychotic properties. The esterification of flupentixol results in the slow release of the drug from the injection site with consequent prolongation of duration of action. The onset of action usually occurs in the range of 24 to 72 hours after injection and the improvement of symptoms continues for two to four weeks. However, there is considerable variation in the individual response of patients to flupentixol decanoate and its use for maintenance therapy requires careful supervision.

The exact mechanism of action of flupentixol has not been established. Its effects resemble those of the phenothiazine, fluphenazine, in that it belongs among the antipsychotic drugs which are less likely to cause sedation and hypotension, but have greater propensity for producing extrapyramidal reactions.

Pharmacokinetics: In pharmacokinetic studies measuring flupentixol blood levels, peak concentrations of the drug were found between days 4 and 7, following intramuscular injections of 40 mg of flupentixol decanoate 2% or 10%. It could still be detected in the blood three weeks after injection. The metabolites of flupentixol appear to be inactive.

INDICATIONS

Flupentixol Decanoate Injection BP (flupentixol decanoate) is indicated in the maintenance therapy of chronic schizophrenic patients whose main manifestations do not include excitement, agitation or hyperactivity.

CONTRAINDICATIONS

Flupentixol decanoate is contraindicated in patients with known hypersensitivity to the thioxanthenes. The possibility of cross-sensitivity between the thioxanthenes and phenothiazine derivatives should be considered.

Flupentixol decanoate is also contraindicated in the presence of CNS depression due to any cause, comatose states, suspected or established subcortical brain damage, blood dyscrasias, pheochromocytoma, liver damage, cerebrovascular or renal insufficiency, and severe cardiovascular disorders. It is not indicated for the management of severely agitated psychotic patients, psychoneurotic patients or geriatric patients with confusion and/or agitation. As with

phenothiazines, flupentixol decanoate should not be used concomitantly with large doses of hypnotics due to the possibility of potentiation.

WARNINGS AND PRECAUTIONS

Tardive Dyskinesia: Tardive dyskinesia is a neurological syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that may develop in patients receiving treatment with antipsychotic drugs (see **ADVERSE REACTIONS**). Although the syndrome appears to be most prevalent in the elderly, especially elderly female patients, it is impossible to predict at the onset of treatment which patients are likely to develop tardive dyskinesia.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible increase with the total cumulative dose of the antipsychotic agent and the duration of treatment. However, less commonly, the syndrome can develop after relatively brief periods of treatment at low doses. Although there is no established treatment of tardive dyskinesia, the syndrome may remit, partially or completely, following withdrawal of the antipsychotic drug. Antipsychotic treatment may itself suppress the signs and symptoms of tardive dyskinesia, possibly masking the underlying process. However, the effects of symptomatic suppression on the long-term course of the syndrome are not known.

In view of these considerations, Flupentixol Injection BP should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. As with any antipsychotic drug, Flupentixol Injection BP should be administered at the smallest dose and for the shortest duration of treatment that is consistent with a satisfactory clinical response. Chronic use should be reserved for patients who appear to be obtaining a substantial benefit from the drug. The need for continued treatment should be reassessed at periodic intervals.

If the signs and symptoms of tardive dyskinesia develop during treatment with flupentixol decanoate, withdrawal of the drug should be considered. However, some patients may require continued antipsychotic treatment despite the presence of this syndrome.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with neuroleptic drugs (see **ADVERSE REACTIONS**). The clinical manifestations of neuroleptic malignant syndrome are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregularity of pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. Cases in which the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms should be identified. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system pathology.

The management of neuroleptic malignant syndrome should include the immediate discontinuation of antipsychotic drugs and nonessential concurrent therapies. Intensive symptomatic treatment and medical monitoring is required. Concomitant serious medical problems for which specific treatments are available should be dealt with appropriately. No general agreement exists regarding specific pharmacological treatment regimens for uncomplicated neuroleptic malignant syndrome.

If a patient requires antipsychotic drug treatment following recovery from neuroleptic malignant syndrome, the potential reintroduction of drug therapy should be carefully considered. As recurrences of neuroleptic malignant syndrome have been reported, careful patient monitoring is necessary.

Use in Pregnancy: The safety of Flupentixol Injection BP in pregnancy has not been established. Therefore, it should not be administered to women of childbearing potential or during lactation, unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the fetus or child.

Use in Children: Since the safety and efficacy of Flupentixol Injection BP in children have not been established, its use is not recommended in the pediatric age group.

Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Therefore, the evaluation of tolerance and response, and establishment of adequate maintenance therapy require careful stabilization of each patient under continuous, close medical observation and supervision.

Flupentixol Injection BP is not recommended for excitable, overactive or manic patients, and the relative lack of sedating effect may cause restlessness and insomnia. The drug should be used with caution in patients with parkinsonism or severe arteriosclerosis.

Although flupentixol is a relatively non-sedating drug, sedation may occur in some patients. Therefore, ambulatory patients should be warned about engaging in activities such as driving a car or operating machinery and about the concomitant use of alcohol and other CNS depressant drugs, since potentiation of their effects may occur.

Flupentixol decanoate should be used with caution in patients with a history of convulsive disorders since it may lower the convulsive threshold.

The possibility of the development of irreversible dyskinesia should be borne in mind when patients are on prolonged therapy.

The antiemetic effect observed with flupentixol in animal studies may also occur in man; therefore, the drug may mask signs of toxicity due to overdosage of other drugs, or it may mask the symptoms of disease, such as brain tumour or intestinal obstruction.

Although its anticholinergic properties are relatively weak, flupentixol decanoate should be used with caution in patients who are known or are suspected to have glaucoma, and in those patients

who might be exposed to extreme heat, or organophosphorus insecticides or who are receiving atropine or related drugs. Paralytic ileus has occasionally been reported, particularly in the elderly, when several drugs with anticholinergic effects have been used simultaneously.

Blood dyscrasias and liver damage have been reported with this class of drugs, but only eosinophilia to date with flupentixol. Therefore, routine blood counts and hepatic function tests are advisable, particularly during the first months of therapy. Should either of these disorders occur, supportive treatment should be instituted and the drug discontinued.

Photosensitivity reactions, pigmentary retinopathy, and lenticular and corneal deposits, although not reported to date with flupentixol, have been reported with related drugs.

Caution should be observed when using a drug of this category in patients who may have a propensity for development of defects in cardiac conduction.

Patients on large doses of flupentixol decanoate who are undergoing surgery should be watched carefully for possible hypotensive phenomena, and anesthetic or central nervous system depressant drug dosages may have to be reduced.

To lessen the likelihood of adverse reactions related to drug accumulation, patients on long-term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage can be lowered or drug therapy discontinued.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies, nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumourigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS

The most common adverse reactions reported with flupentixol decanoate have been extrapyramidal symptoms, occurring in up to 30% of patients.

Flupentixol shares many of the pharmacologic properties of other thioxanthenes and phenothiazines. Therefore, the known adverse reactions of these drugs should be borne in mind when Flupentixol Injection BP is used.

Central Nervous System: Extrapyramidal symptoms, including hypo- and hyperkinetic states, tremors, pseudoparkinsonism, dystonia, hypertonia, akathisia, oculogyric crises, opisthotonos,

hyperreflexia and tardive dyskinesia (see **WARNINGS** and below). The symptoms, if they are to occur, usually appear within the first few days of a drug administration and can usually be controlled or totally curtailed by reduction in dosage and/or standard anticholinergic antiparkinsonian medication. The incidence of extrapyramidal symptoms appears to be more frequent with the first few injections of Flupentixol Injection BP, and diminishes thereafter. The routine prophylactic use of antiparkinsonian medication is not recommended. Extrapyramidal reactions may be alarming, and patients should be forewarned and reassured.

Other CNS effects reported with flupentixol decanoate include restlessness, insomnia, overactivity, psychomotor agitation, hypomania, epileptiform convulsions, headache, drowsiness, somnolence, depression, fatigue, and anergia.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of fifty. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop (see **WARNINGS**).

Autonomic Nervous System: Dry mouth, blurred vision, constipation, excessive salivation, excessive perspiration, nausea, difficulty in micturition, dizziness, palpitations and fainting have been observed with flupentixol decanoate but are uncommon. Miosis, mydriasis, paralytic ileus, polyuria, nasal congestion, glaucoma, tachycardia, hypotension, hypertension, fluctuations in blood pressure, nonspecific ECG changes and cardiac arrhythmias have been reported with related drugs. If hypotension occurs, **epinephrine should not be used** as a pressor agent since a paradoxical further lowering of blood pressure may result.

Metabolic and Endocrine: Weight change, galactorrhea, elevation in serum prolactin levels, impotence, loss of libido, and sexual excitement have been reported with flupentixol decanoate. Related drugs have been also associated with breast enlargement, menstrual irregularities, false positive pregnancy tests, peripheral edema, gynecomastia, hypo- and hyperglycemia and glycosuria.

Toxic and Allergic: Eosinophilia, jaundice and increased levels of SGOT, SGPT and alkaline phosphatase have been reported with flupentixol. Other antipsychotic drugs have been associated with leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, hemolytic anemia and pancytopenia. If any soreness of the mouth, gums or throat or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Skin reactions, such as pruritus, rash, urticaria, erythema, seborrhea, eczema, exfoliative dermatitis, and contact dermatitis have been reported with flupentixol or related drugs. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

Miscellaneous: Sudden, unexpected and unexplained deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behaviour patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions.

The following adverse reactions have also occurred with phenothiazine derivatives: photosensitivity, systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema. Skin pigmentation, and lenticular and corneal opacities have been seen with long-term use of phenothiazines.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a drug overdose contact your regional Poison Control Centre.

Overdosage is characterized by sedation, frequently preceded by extreme agitation, excitement and confusion. Extrapyramidal symptoms may develop, and respiratory and circulatory collapse may occur.

Treatment is symptomatic. No further injections should be given until the patient shows signs of relapse and the dosage then should be decreased. An airway should be maintained. Severe hypotension calls for the immediate use of an I.V. vasopressor drug, such as levarterenol. Epinephrine should **not** be used as a further lowering of blood pressure may result. Antiparkinsonian medication should be administered only if extrapyramidal symptoms develop.

DOSAGE AND ADMINISTRATION

Flupentixol Decanoate Injection BP (flupentixol decanoate) is administered by deep intramuscular injection, preferably in the gluteus maximus. Flupentixol Decanoate Injection BP is **not** for intravenous use.

As a long-acting depot preparation, flupentixol decanoate has been found useful in the maintenance treatment of nonagitated chronic schizophrenic patients who have been stabilized with short-acting neuroleptics and might benefit from transfer to a longer acting injectable medication. The changeover of medication should aim at maintaining a clinical outcome similar to or better than that obtained with the previous therapy. To achieve and maintain the optimum dose, the changeover from other neuroleptic medication should proceed gradually and constant supervision is required during the period of dosage adjustment in order to minimize the risk of overdosage or insufficient suppression of psychotic symptoms before the next injection.

Patients not previously treated with long-acting depot neuroleptics should be given an initial test dose of 5 mg (0.25 mL) to 20 mg (1.0 mL) of Flupentixol Decanoate Injection BP 2%. An initial dose of 20 mg (1.0 mL) of Flupentixol Decanoate Injection BP 2% is usually well tolerated; however, a 5 mg (0.25 mL) test dose of Flupentixol Decanoate Injection BP 2% is recommended in elderly, frail and cachectic patients; and in patients whose individual or family history suggests a predisposition to extrapyramidal reactions. In the subsequent five to ten days, the therapeutic response and the appearance of extrapyramidal symptoms should be carefully monitored. Oral neuroleptic drugs may be continued, but in diminishing dosage, during this period.

In patients previously treated with long-acting depot neuroleptics who displayed good tolerance to these drugs, an initial dose of 20 to 40 mg (1.0 to 2.0 mL) of Flupentixol Decanoate BP 2% may be adequate.

Subsequent doses and the frequency of administration must be determined for each patient. There is no reliable dosage comparability between a shorter acting neuroleptic and depot flupentixol, and, therefore, the dosage of the long-acting drug must be individualized.

Except in particularly sensitive patients, a second dose of 20 (1.0 mL) to 40 mg (2.0 mL) of Flupentixol Decanoate Injection BP 2% can be given 4 to 10 days after the initial injection. Subsequent dosage adjustments are made in accordance with the response of the patient, but the majority of patients can be adequately controlled by 20 to 40 mg (1.0 to 2.0 mL) of Flupentixol Decanoate Injection BP 2% every two to three weeks. The optimal amount of the drug has been found to vary with the clinical circumstances and individual response. Doses greater than 80 mg (4.0 mL) of Flupentixol Decanoate Injection BP 2% are usually not deemed necessary, although higher doses have been used occasionally in some patients.

Although the response to a single injection usually lasts for two to three weeks, it may last for four weeks or more, particularly when higher doses are used. Since higher doses increase the incidence of extrapyramidal reactions and other adverse effects, the amount of drug used should not be increased merely in order to prolong the intervals between injections. With higher doses there may also be more variability in the action of Flupentixol Decanoate Injection BP and, therefore, unit dose increments should not exceed 20 mg (1.0 mL) of Flupentixol Decanoate Injection BP 2%. After an appropriate dosage adjustment is achieved, regular and continuous supervision and reassessment is considered essential in order to permit any further dosage

adjustments that might be required to ensure use of the lowest effective individual dose and avoid troublesome side effects.

Patients who require higher doses of Flupentixol Decanoate Injection BP to control symptoms of schizophrenia and/or those who complain of discomfort with a large injection volume may be administered Flupentixol Decanoate Injection BP 10% (100 mg/mL) in preference to Flupentixol Decanoate Injection BP 2% (20 mg/mL).

AS WITH ALL OILY INJECTIONS IT IS IMPORTANT TO ENSURE, BY ASPIRATION BEFORE INJECTION, THAT INADVERTENT INTRAVASCULAR INJECTION DOES NOT OCCUR.

PHARMACEUTICAL INFORMATION

Drug Substance

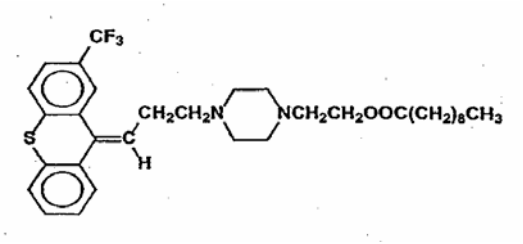
Proper Name: Flupentixol Decanoate BP

Chemical Name: (Z)-2-{4-[3-(2-trifluoromethylthioxanthen-9-ylidene) propyl]piperazin-1-yl}ethyl decanoate.

Molecular Formula: $C_{33}H_{43}F_3N_2O_2S$

Molecular Mass: 588.82 g/mol

Structural Formula:



Physicochemical Properties: A yellow viscous oil.

Water: Very slightly soluble

Ethanol: Soluble

Ether and Chloroform: Freely soluble

AVAILABILITY OF DOSAGE FORMS

Each mL of Flupentixol Decanoate Injection BP 2% contains 20 mg of flupentixol decanoate in vegetable oil [medium-chain triglycerides (coconut oil)].

Each mL of Flupentixol Decanoate Injection BP 10% contains 100 mg of flupentixol decanoate in vegetable oil [medium-chain triglycerides (coconut oil)].

Flupentixol Decanoate Injection BP 2% is supplied in 10 mL amber vials, boxes of 1.

Flupentixol Decanoate Injection BP 10% is supplied in 2 mL amber vials, boxes of 1.

LATEX-FREE STOPPER: Stopper contains no dry natural rubber.

Multidose vials. Discard unused portion 6 months after initial puncture.

STABILITY AND STORAGE

Flupentixol Decanoate Injection BP should be stored between 15 and 30°C and protected from light. Keep out of reach of children.

INSTRUCTION FOR USE: As with all parenteral drug products, the injection should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

INFORMATION FOR THE CONSUMER

Please read this information leaflet carefully before you start your medicine, even if you have taken this drug before. Keep this leaflet handy in order to consult while taking your medication. For further information or advice, please contact your doctor or pharmacist.

What is Flupentixol Decanoate Injection BP?

- Flupentixol Decanoate Injection BP is a long acting prescription medicine that belongs to a family of medicines used to treat schizophrenia.
- You have been prescribed flupentixol decanoate by injection, it will be administered by a doctor or nurse. Flupentixol decanoate is effective when administered as infrequently as once every 2-3 weeks.
- Flupentixol decanoate is not recommended for children.

What do I need to do before taking Flupentixol Decanoate Injection BP?

Tell your doctor:

- About all your past and present medical conditions, including glaucoma, history of irregular heart rhythms and breast cancer.
- If you have used flupentixol decanoate or any other treatment for schizophrenia before and if you had any problems.
- If you are taking any other prescription or non-prescription medicines, especially hypnotic and sedative drugs.
- If you need surgery, be sure to tell every doctor you consult that you are taking flupentixol decanoate injections.
- If you are pregnant or thinking of becoming pregnant, or if you are breast-feeding. Flupentixol decanoate should not be given to women of childbearing age or who are breast feeding unless the doctor thinks the expected benefit to the patient outweighs the potential risk to the fetus or child.
- If you regularly drink a lot of alcohol.
- If you have any liver problems, kidney disease, severe heart problems, brain damage, severe blockage of some arteries, Parkinson's disease or have ever had seizures.
- If you have ever had any blood disorders.
- If you are allergic to flupentixol decanoate, (the common name for Flupentixol Decanoate BP) or any of the ingredients in Flupentixol Decanoate Injection BP, (i.e. medium chain triglycerides, coconut oil) or thioxanthenes or other phenothiazine types of medications.

How do I take Flupentixol Decanoate Injection BP properly?

Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Therefore, the evaluation of tolerance and response, and establishment of adequate maintenance therapy require careful stabilization of each patient under continuous, close medical observation and supervision.

- You have been prescribed flupentixol decanoate by injection, it will be given by a doctor or nurse. It is very important to keep your scheduled appointments for the injections.
- If you miss an appointment, contact your doctor as soon as possible in order to schedule a new appointment.
- Consult your doctor before taking other medications, including over-the-counter medicines. Some drugs can produce additional side-effects when they are used in combination with flupentixol decanoate including alcohol and sleeping pills or sedatives.

What are some of the Side Effects of Flupentixol Decanoate Injection BP?

Like all medications, flupentixol decanoate can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Consult your doctor if you experience these or other side effects.

Side-effects that have been reported by patients taking flupentixol decanoate include:

- An allergic reaction, if you experience fever (increased temperature) or soreness of the mouth, gums, or throat that happens while you are taking flupentixol decanoate contact your doctor **immediately.**
- At the beginning of treatment, flupentixol decanoate may make you feel drowsy or sleepy so you should not drive a car or operate machinery until you are sure flupentixol decanoate does not affect your mental alertness.
- Muscle spasm, stiffness, shaking or uncontrolled body movements may indicate you have a syndrome called Tardive Dyskinesia. These can happen in different parts of the body, such as the tongue, face, mouth, jaw, eyes, hands, arms and legs. Small uncontrollable movements of the tongue may be an early sign of the syndrome. If the medication is stopped when these symptoms are noticed, the syndrome may not develop further. Tardive Dyskinesia can sometimes be permanent, even if you stop taking flupentixol decanoate. Contact your doctor immediately if this happens to you.
- Other possible side-effects include dry mouth, dizziness, blurred or altered vision, constipation, excessive salivation or sweating, trouble passing urine. Decreases in blood pressure, increases in heart rate, weight changes, skin rash, decreased sexual interest or function, and changes in your monthly cycle (if you are female).
  Tell your doctor or pharmacist if you think you have any of these or other effects while taking flupentixol decanoate.
- A serious condition called Neuroleptic Malignant Syndrome has been reported with the use of drugs like flupentixol decanoate. Symptoms include fever, stiff muscles, confusion, reduced consciousness, irregular heart rate and sweating. Go to the nearest Emergency Room of a hospital if you think this is happening to you.

You should also tell your doctor if you notice any symptoms that worry you, even if you think the problems are not connected with the medicine or are not listed here.

What if I miss a dose or experience an overdose?

- Flupentixol decanoate is given under the supervision of a qualified physician. An overdose or missed dose should be managed by a qualified physician experienced in the use of the intramuscular injections.

Where should I store Flupentixol Decanoate Injection BP?

• Flupentixol Decanoate Injection BP vials should be kept in a safe place between 15°C and 30°C, protected from light. Multidose vials. Discard unused portion 6 months after initial puncture.
• Keep Flupentixol Decanoate Injection BP out of the reach of children.
• Safely discard any Flupentixol Decanoate Injection BP that has passed the expiry date on the label.

Who do I ask if I have any questions about Flupentixol Decanoate Injection BP?

• Consult your doctor or pharmacist. You may also contact the manufacturer, Sandoz Canada Inc.(the address is at the end of this leaflet).

What does Flupentixol Decanoate Injection BP contain?

• Flupentixol Decanoate Injection BP contains flupentixol decanoate as the active ingredient in vegetable oil (coconut oil).

Who supplies Flupentixol Decanoate Injection BP?

Flupentixol Decanoate Injection BP is supplied by:

Sandoz Canada Inc.
145 Jules-Léger
Boucherville, QC, Canada
J4B 7K8

1-800-361-3062

REMINDER: Flupentixol Decanoate Injection BP has been prescribed only for you. Do not give it to anybody else.

PHARMACOLOGY

Flupentixol reduces spontaneous activity in mice and induces a cataleptic state as determined by the vertical rod test. The drug antagonizes amphetamine-induced stereotyped behaviour and apomorphine-induced compulsive gnawing in rats as well as methylphenidate-induced compulsive gnawing in mice. It is also effective in preventing apomorphine-induced emesis in dogs.

Flupentixol inhibits the conditioned and, at higher doses, the unconditioned avoidance response in rats. It is also effective in releasing conflict-suppressed behaviour in rats.

Flupentixol provides some protection against amphetamine-induced stimulation and potentiates barbiturate-induced sleep. It protects rats against isoniazid and pentetrazol convulsions, and, in higher doses, against electroconvulsions.

Flupentixol displays very weak anticholinergic activity in isolated guinea pig ileum and weak adrenolytic activity. It does not inhibit monoamine oxidase, nor does it inhibit the reuptake of adrenergic transmitters of adrenergic nerve endings.

Flupentixol antagonizes the effect of dopamine on cyclic AMP in the olfactory tubule and nucleus accumbens in the rat and antagonizes the dopamine agonist 2-amino-6,7-dihydroxy-

1,2,3,4-tetrahydronaphtalene in the striatum. With the exception of minor drops in blood pressure seen when the drug is given by the intravenous route, it is without effect on the cardiovascular system of dogs. Blood pressure was also reduced by flupentixol in anesthetized rats and cats.

Like most other neuroleptics, flupentixol inhibits the prolactin-inhibiting factor, resulting in an increase in serum prolactin levels.

Pharmacokinetics: Studies in rats and dogs with ^{3}H-flupentixol decanoate have revealed that flupentixol decanoate diffuses slowly from the oil solution into the extracellular fluid from where it is distributed *via* the blood stream to the different tissues of the body. The half-life of the drug calculated from excretion data has been shown to be eight days for the rat and about 12 days for the dog. Peak serum levels occur within the first 24 hours in rats and at 7 days after injection in dogs, but significant levels of radioactivity are found up to five weeks after administration. Flupentixol decanoate is efficiently hydrolized *in vivo* to flupentixol which is present in all tissues of the body.

The highest levels of flupentixol as reflected by radioactivity count are found in the lungs, liver, and spleen, while concentrations in the brain are considerably lower, and only a little higher than concentrations found in the blood. Flupentixol is metabolized by sulfoxidation, dealkylation (splitting of the distal ethanolic group in the side chain) and conjugation to glucuronic acid. The more hydrophilic compounds, sulfoxides and glucuronides are excreted with urine, the more lipophilic ones, flupentixol and dealkyl-flupentixol, with feces. Quantitatively, the fecal excretion dominates. The metabolites of flupentixol are devoid of psychopharmacological activity.

TOXICOLOGY

The parenteral LD_{50} of flupentixol decanoate is greater than 200 mg/kg in rats. Mice administered 400 mg/kg orally or parenterally survived for three days. The majority died between the fourth and tenth day after becoming sedated and being unable to eat or drink.

10 or 15 mg/kg of flupentixol decanoate was administered twice weekly to rats for seven weeks. It was associated with some inhibition of growth secondary to sedation causing reduced food intake, a decrease in red blood cells (males only), and an increase in serum creatinine. At postmortem, the only significant finding, apart from a slight decrease in liver weight in males, was a localized subcutaneous reaction around the oil droplets. During a ten-week recovery period the oil droplets disappeared gradually, but not completely.

Dogs were administered 0, 2 and 6 mg/kg/week intramuscularly for 26 weeks. The only significant findings were a heavy local reaction with some encapsulated small oil drops at the injection site, slight swelling of the popliteal gland (16th week), some inter- and intramuscular fibrosis with hyperplasia of the popliteal lymph node and an apparently dose-related transient increase in alpha-globulins with concurrent decrease in beta and gamma globulins.

Reproductive Studies: Flupentixol decanoate was administered on day 6 of gestation to mice and rats (10 and 20 mg/kg S.C.) and to rabbits (2 and 6 mg/kg I.M.). Dams were not adversely affected. However, an abortifacient effect occurred in mice receiving 20 mg/kg.

In reproductive studies with flupentixol hydrochloride, a similar abortifacient effect was noted in mice and rabbits. In rats, fetotoxic effects (reduced conception rates, increased resorptions, retarded growth and poor weaning performances) were observed. Four cases of cleft palate were found in three litters of rats receiving 50 or 25 mg/kg/day.

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