PRODUCT MONOGRAPH

FLUPHENAZINE DECANOATE INJECTION B.P.

Fluphenazine Decanoate Injection
25mg/mL

Fluphenazine Decanoate Injection Concentrate
100mg/mL

Antipsychotic

Hospira Healthcare Corporation
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ACTIONS AND CLINICAL PHARMACOLOGY

Fluphenazine exerts activity at various levels of the central nervous system as well as at the peripheral organ systems, which accounts for its antipsychotic action and side effects. Indirect evidence shows that the antipsychotic effects of phenothiazines are linked to their action in blocking dopamine and other catecholamine receptor sites.

Fluphenazine has weak anticholinergic and sedative effects, but it exhibits a greater propensity for producing extrapyramidal reactions than do other phenothiazines such as chlorpromazine. Although hypotension may occur less frequently than with other phenothiazines, appropriate precautions should be observed when using fluphenazine decanoate (see **PRECAUTIONS**).

The actions of fluphenazine decanoate are similar to those of fluphenazine hydrochloride. However the esterification of the active molecule with a long chain fatty acid and the use of an oil vehicle result in the slow release of the decanoate derivative from the site of injection, leading to a prolonged duration of action. On release in the blood, fluphenazine decanoate is rapidly hydrolyzed by blood esterases with no attenuation of its antipsychotic action. The onset of action normally occurs between 24 and 72 hours after injection, and the effects of the drug on psychotic symptoms become significant within 48 to 96 hours. Amelioration of symptoms then continues for 1-8 weeks with an average duration of 3-4 weeks. There is considerable variation in the individual response of patients to this depot fluphenazine; its use for maintenance therapy needs careful supervision.

Fluphenazine decanoate injected intramuscularly produces an early high peak which occurs during the first day and then declines with an apparent half-life ranging from 6.8 to 9.6 days following a single injection. Good correlations between fluphenazine plasma levels and intramuscular drug dosage are seen. After multiple injections of fluphenazine decanoate, the mean apparent half-life increases to 14.3 days, and the time to reach steady-state is 4 to 6 weeks. Withdrawal studies with fluphenazine decanoate suggest that relapsing patients have a more rapid plasma concentration decline than non-relapsing patients, and that the plasma concentrations do not decline smoothly but may exhibit 'lumps' due to residual release from previous injection sites or multicompartment redistribution. Cigarette smoking has been found to be associated with a two-fold increase in the clearance of fluphenazine decanoate.

Fluphenazine dosage correlates poorly with the occurrence of side effects, except that low doses (less than 18.75 mg/week) are associated with minimal side effects.

Fluphenazine and metabolites 7-hydroxyfluphenazine and fluphenazine sulphoxide, are excreted as conjugates in the urine. There is a linear relationship between plasma fluphenazine and the urinary excretion of total drug products. The rate of urinary excretion appears to be independent of the urine pH and volume. Fluphenazine and 7-hydroxyfluphenazine, but no conjugates, are eliminated in feces.

INDICATIONS

Fluphenazine Decanoate Injection B.P., a long acting parenteral preparation, is indicated in the management of manifestations of schizophrenia (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Fluphenazine Decanoate Injection B.P. is contraindicated in:

1. Patients with marked cereberal atherosclerosis, with suspected or established subcortical brain damage, with or without hypothalamic damage, because a hyperthermic reaction with temperatures above 40°C may occur, occasionally not until 14 to 16 hours after drug administration.
2. Patients receiving large doses of hypnotics owing to the possibility of potentiation.
3. Comatose or severely depressed patients.
4. Patients with blood dyscrasias, liver damage, renal insufficiency, pheochromocytoma.
5. Patients with severe cardiovascular disorders.
6. Patients who have shown hypersensitivity to other phenothiazines, including fluphenazine, because cross-sensitivity reactions may occur.
7. The management of severely agitated psychotic, psychoneurotic or geriatric patients with confusion and/or agitation.
8. Children under 12 years of age.

WARNINGS

Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Hence, 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.

Occupational hazards: The mental and physical abilities required for driving a car or operating heavy machinery may be impaired by the administration of this drug. The effects of alcohol may also be potentiated.

Pregnancy: The safety of the drug during pregnancy has not yet been established. The drug should not be administered to women of childbearing potential unless the physician believes that the expected benefits outweigh any potential risk to the fetus, especially in the first trimester.

Children: The drug is not indicated for pediatric use as safety and efficacy have not yet been established in children.

Tardive Dyskinesia (TD): Tardive Dyskinesia is a syndrome associated with involuntary hyperkinetic abnormal movements which occur in predisposed patients during or following the termination of long-term neuroleptic drug therapy. The characteristics of TD are involuntary, repetitive, purposeless hyperkinetic movements which involve the tongue, face, mouth, lips or jaw, the trunk and extremities. The prevalence of TD can vary greatly according to the degree of severity of symptoms. The prevalence can be 70% in the case of the mildest symptoms and 2.5% in the case of severe symptoms. Increases in age results in increases in frequency and severity of TD, especially in women.

It is unknown whether neuroleptic drugs differ in their potential to cause TD, but as a precautionary measure, the interpretation is that any neuroleptic drug which supperesses TD has the ability to produce it. The mechanism of TD is unknown. Dopamine dysfunction is believed to underlie TD but it is not sufficient to explain this complex disorder.

No known treatment for established cases of TD exists, though the syndrome may partially or completely remit if neuroleptic treatment is withdrawn. However, the signs and symptoms of the syndrome are suppressed by the neuroleptic treatment itself, resulting in the masking of the underlying disease process.

Considering the above, the prescription of neuroleptic drugs should be designed to minimize the occurence of TD. The most rational approach continues to be reducing the dose to its lowest effective level or discontinuing the drug for as long as possible. In the case of patients requiring chronic treatment, a regimen with the smallest dose and the shortest duration producing a satisfactory

clinical response is sought. It should be periodically reassessed to determine whether continued treatment is needed.

PRECAUTIONS

Phenothiazines, especially those with a long duration of action, should be used with caution in patients with a history of convulsive disorders as grand mal seizures have been known to occur. Owing to the possibility of cross-sensitivity, caution should be exercised when fluphenazine decanoate is administered to patients with cholestatic jaundice, dermatoses or other allergic reactions to phenothiazine derivatives.

Since blood dyscrasias and liver damage, manifested by cholestatic jaundice may occur, routine blood counts and hepatic function tests are advised, particularly during the initial months of therapy. In patients on long-term therapy, renal function should be monitored; should the blood urea nitrogen (BUN) become abnormal, treatment should be discontinued.

A hypotensive phenomenon may occur in phenothiazine-treated patients who are undergoing surgery. Careful observation is essential, and dosages of anesthetic or central nervous system depressants may have to be reduced.

Phenothiazines possess an anticholinergic activity and therefore enhance the anticholinergic properties of drugs such as atropine and tricyclic anti-depressants. Paralytic ileus, which may be fatal, may occur, particularly in the elderly. Fluphenazine decanoate should be used with care in patients exposed to extreme heat or phosphorus insecticides.

As with other antipsychotic agents, the physician should be alert to the possible development of silent pneumonias in patients under phenothiazine therapy. Moreover, when patients are placed under prolonged treatment, the possibility of liver damage, lenticular and corneal deposits,

pigmentary retinopathy, as well as the development of irreversible dyskinesia, should be borne in mind.

Caution should be exercised when fluphenazine decanoate is used in patients with compensated cardiovascular or cerebrovascular disorders since hypotension and electrocardiographic alterations suggestive of myocardial ischemia have been associated with the administration of phenothiazines.

Prolactin levels are elevated by neuroleptic drugs. These elevated levels persist during chronic administration. The results of tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependant in vitro. This is a factor of potential importance should the prescription of neuroleptic drugs be considered in a patient with a previously detected breast cancer. In the case of most patients, the clinical significance of elevated serum prolactin levels is unknown. However, occurances such as galactorrhea, amenorrhea, gynocomastia, and impotence have been reported. Chronic administration of neuroleptic drugs has resulted in increased mammary neoplasms in rodents. However, neither clinical nor epidemiologic studies conducted to date have shown any association between chronic administration of neuroleptic drugs and mammary tumorigenesis. No conclusion has been drawn as yet due to the limited nature of the available evidence.

ADVERSE REACTIONS

Central Nervous System

Extrapyramidal symptoms: The side effects most commonly reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, oculogyric crises, dystonia, dyskinesia, akathisia, opisthotonos and hyperreflexia.

A higher incidence of extrapyramidal reactions is produced with fluphenazine decanoate than with the less potent piperazine derivatives or straight-chain phenothiazines such as chlorpromazine. The extrapyramidal reactions have a tendancy to occur within the first few days following an injection.

Caution should be exerted in individuals with marked extrapyramidal reactions to oral phenothiazines or similar drugs, especially in elderly females. The patient should be forewarned and reassured as the extrapyramidal reactions may be alarming. The extrapyramidal reactions are frequently dose related and will tend to subside when the dose is reduced or temporarily discontinued. However, serious reactions may be controlled by antiparkinsonian medication.

Even though the therapeutic value of the use of prophylactic antiparkinsonian medication has not yet been established, its use may be considered.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may develop in some patients on long-term therapy or after drug therapy has been reduced or discontinued.

The risk appears to be more in elderly patients on high dose therapy, particularly females. The symptoms are persistent and seem to be irreversible in certain patients. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puckering of mouth, chewing movements, puffing of cheeks). These may occasionally be accompanied by involuntary movements of the extremities.

No effective treatment for tardive dyskinesia is known, antiparkinsonian agents do not normally alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms occur. Reinstituting treatment, increasing the dosage of the drug, or switching to another antipsychotic drug, may mask the syndrome. It may be possible for the physician to reduce the risk of this syndrome by minimizing the use of neuroleptic drugs, reducing the dose or discontinuing the drug if possible, especially in patients over the age of fifty. Fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is discontinued at that time, the syndrome may not develope.

The prescription of neuroleptic drugs should be designed to minimize the occurence of tardive dyskinesia. The most rational approach continues to be reducing the dose to its lowest effective level or discontinuing the drug for as long as possible. In the case of patients requiring chronic treatment,

a regimen with the smallest dose and the shortest duration producing a satisfactory clinical response is sought. It should be periodically reassessed to determine whether continued treatment is needed.

Neuroleptic malignant syndrome: On rare occasions, patients on neuroleptic drugs have reported neuroleptic malignant syndrome (NMS). Characteristics of NMS are hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia and altered consciousness, occasionally progressing to stupor or coma. Other adverse effects may include leukocytosis, elevated CPK, liver function abnormalities and acute renal failure. Since NMS is a potentially fatal syndrome, neuroleptic therapy should be immediately discontinued and vigorous symptomatic treatment begun.

Other CNS effects: If drowsiness and lethargy occur, it may be necessary to reduce the dosage of the drug. High doses of fluphenazine have been known to induce a catatonic-like state. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered.

In some patients, phenothiazine derivatives have been known to cause excitement, restlessness or bizarre dreams.

Autonomic Nervous System

Hypotension, hypertension and fluctuations in blood pressure have been reported with fluphenazine. Patients suffering from pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency, are especially prone to hypotensive reactions with phenothiazine compounds. Supportive measures including the use of intravenous vasopressor drugs should be instituted at once should severe hypotension occur. Norepinephrine Bitartrate Injection is the drug of choice for this purpose; **epinephrine should not be used** since phenothiazine derivatives have been reported to reverse its action, leading to a further reduction of blood pressure. Autonomic reactions such as nausea and loss of appetite, salivation, dry mouth, perspiration, polyuria, headache and constipation may occur. Such autonomic effects can normally be controlled by decreasing dosage or temporarily withdrawing the drug.

Phenothiazine derivatives have been known to cause glaucoma, blurred vision, bladder paralysis, fecal impaction, paralytic ileus, nasal congestion or tachycardia in certain patients.

Metabolic and Endocrine

Peripheral edema, change in weight, gynecomastia, menstrual irregularities, false results on pregnancy tests, abnormal lactation, increased libido in women, and hypersexuality or impotence in men have occurred in some patients on phenothiazine therapy.

Allergic Reactions

Skin disorders including itching, urticaria, erythema, seborrhea, eczema, exfoliative dermatitis and photosensitivity have occurred with phenothiazine derivatives. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic

Agranulocytosis, leukopenia, thrombocytopenic or non-thrombocytopenic purpura, eosinophilia and pancytopenia have been observed with phenothiazine derivatives. Therapy should be discontinued and other appropriate measures instituted immediately if any soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte counts indicate cellular depression.

Hepatic

Liver damage, as manifested by cholestatic jaundice, may be observed, especially during the initial months of treatment. If this occurs, treatment should be withdrawn. An increase in cephalin flocculation, sometimes accompanied by changes in other liver function tests, has been reported in patients administered with fluphenazine enanthate (a closely related compound); these patients have had no clinical evidence of liver damage.

Others

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Flare-ups of psychotic behavior patterns have been seen in some patients shortly before death. Autopsy findings have normally revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions. Potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

Other adverse reactions known to occur with phenothiazine derivatives include: systemic lupus erythematosus-like syndrome, hypotension sufficiently severe to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, disturbances of body temperature (hypo/hyperthermia), laryngeal edema, asthma and angioneurotic edema. The neuroleptic malignant syndrome may occur, particularly in patients with brain damage. Skin pigmentation, and lenticular and corneal opacities have been seen with prolonged use.

Injections of fluphenazine decanoate are well tolerated, local tissue reactions occurring only rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Likely to be observed are extrapyramidal signs, sedation and hypotension. Initial hospitalization may be necessary in cases of large overdose and close medical supervision should be maintained throughout the duration of drug action.

Treatment: Involves supportive and symptomatic care; no further injections should be administered until the patient shows signs of relapse and the dosage then should be reduced.

An airway should be maintained. Severe hypotension should be treated immediately with an intravenous vasopressor drug such as Norepinephrine Bitartrate Injection. Epinephrine should **not** be used since it may lead to a further lowering of blood pressure. Extrapyramidal symptoms may be treated with appropriate antiparkinsonian drugs such as Benztropine Mesylate.

DOSAGE AND ADMINISTRATION

Fluphenazine Decanoate Injection is normally given intramuscularly, preferably in the gluteus maximus, although it may also be administered subcutaneously. Fluphenazine Decanoate Injection is not for intravenous use.

As a long-acting depot injection, Fluphenazine Decanoate Injection has been found useful in the maintenance therapy of non-agitated, chronic schizophrenic patients who have been stabilized with short-acting neuroleptics. Such patients may benefit from transfer to a longer-acting injectable medication. The changeover of medication ought to aim at maintaining a clinical outcome similar to, or better than, that obtained with the previous therapy. To achieve and maintain the optimum dosage, the changeover from other neuroleptic medication should proceed gradually. Constant monitoring is necessary during the period of dosage adjustment so as to minimize the risk of overdosage or insufficient suppression of psychotic symptoms prior to the next injection.

The initial recommended dose is 2.5 mg to 12.5 mg. An initial dose of 12.5 mg is normally well tolerated. Nevertheless, an initial test dose of 2.5 mg is recommended in patients:

(a) over the age of 50 or with disorders which predispose to undue reactions;

(b) whose individual or family history suggests a predisposition to extra-pyramidal reactions;

(c) who have not previously received a long-acting depot neuroleptic.

The onset of action of the drug generally occurs from between 24 to 72 hours following injection. The effects on psychotic symptoms become significant within 48 to 96 hours.

Discontinuation of oral neuroleptic medication has been recommended for up to one week before initiation of depot fluphenazine therapy.

Subsequent doses and frequency of administration must be determined on an individual basis. There is no reliable dosage comparability between a shorter-acting phenothiazine and depot fluphenazine and, therefore, the dosage of the long-acting drug must be individualized.

Except in especially sensitive patients, a second dose of 12.5 mg or 25 mg can be administered 4 to 10 days after the initial injection.

Subsequent dosage adjustments are made according to the clinical circumstances and the response of the patient.

Patients can normally be controlled with 25 mg or less, every two to three weeks. Doses up to 100 mg have been used in some patients although doses more than 50 mg are usually not deemed necessary. Should doses greater than 50 mg become necessary, the next dose and succeeding doses should be administered in increments of 12.5 mg. Even though the response to a single injection normally lasts two to three weeks, it is possible that it may last for four weeks or more.

The dosage of drug used should not be increased in order to prolong the intervals between injections as higher doses increase the incidence of extrapyramidal reactions and other adverse effects. There is also more variability, with higher doses, in the action of depot fluphenazine.

After an appropriate dosage adjustment is achieved, regular and continuous monitoring and reassessment is considered necessary in order to allow any further dosage adjustments that may be required to ensure use of the lowest effective individual dose and to avoid troublesome side-effects. A dry syringe with a needle of at least 21 gauge should be used to inject Fluphenazine Decanoate Injection. Use of a wet needle or syringe may cause the solution to become cloudy.

The 100 mg/mL concentration of Fluphenazine Decanoate Injection is recommended for patients who suffer discomfort when a large injection volume is administered, or in other cases when a smaller injection volume is desirable.

PHARMACEUTICAL INFORMATION

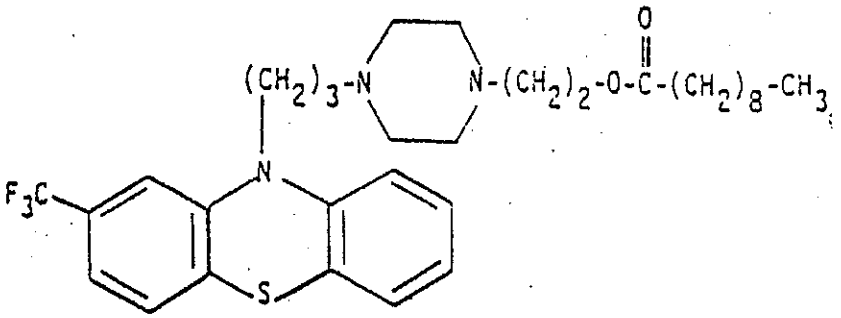
Drug Substance

Proper name: Fluphenazine Decanoate

Chemical name: BP: 2-{4-[3-(2-Trifluoromethylphenothiazin-10-yl) propyl]-piperazin-1-yl} ethyl decanoate.

CAS: 69-23-8 (fluphenazine) 5002-47-1 (decanoate).

Structural formula:



Molecular formula: $C_{32}H_{44}F_3N_3O_2S$

Molecular weight: 591.8

Description: Fluphenazine decanoate is a pale yellow viscous liquid or a yellow crystalline oily solid with a faint ester-like odor. It is practically insoluble in water and is light-sensitive.

Composition: Each mL of **Fluphenazine Decanoate Injection, 25 mg/mL,** contains 25 mg of fluphenazine decanoate B.P. in sesame oil, with benzyl alcohol 1.2% w/v as preservative.

Each mL of **Fluphenazine Decanoate Injection Concentrate, 100 mg/mL,** contains 100 mg of fluphenazine decanoate B.P. in sesame oil, with benzyl alcohol 1.5% w/v as preservative.

Stability and storage recommendations:

Store between 15 - 25°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Fluphenazine Decanoate Injection, 25 mg/mL, is available in multi-dose vials containing 125 mg/5 mL fluphenazine decanoate B.P.

Fluphenazine Decanoate Injection Concentrate, 100 mg/mL, is available in ampoules containing 100 mg/1 mL fluphenazine decanoate B.P. This concentration is recommended for patients who suffer discomfort when a large injection volume is administered, or in other cases when a smaller injection volume is desirable.

ANIMAL PHARMACOLOGY

Fluphenazine inhibited the head-twitch response in mice with maximal inhibitory effect 3 to 6 hours after dosage. Fluphenazine produced moderate to marked inhibition of the conditioned avoidance response in rats for at least 24 hours after administration of a median dose of 0.5 mg/kg. The drug exhibited a tranquilizing effect on hostile Rhesus monkeys and on the operant behaviour of rats exposed to a shock-avoidance schedule.

Fluphenazine reduced spontaneous motor activity, caused sedation and ataxia and decreased rectal temperature in dogs. Cumulative, intravenous doses of fluphenazine caused slight to moderate hypotension in anesthetized and unanesthetized dogs.

No significant changes in ECG were noted after administration of fluphenazine to curarized cats, but marked transient hypotension followed cumulative, intravenous, total doses of 16 to 32 mg/kg. Total dosage of 64-128 mg/kg caused cardiac arrest. Cumulative doses exceeding 8 mg/kg caused progressive bradycardia.

^{14}C-labelled fluphenazine enanthate and decanoate in sesame oil solution were administered intramuscularly to dogs. Based on the ^{14}C-activity determined over a period of 35 days, the average plasma half-life for the former was approximately 9 days and for the latter, 33 days; again, the urinary, fecal, and total elimination half-lives were about one-half as long with the enanthate as they were with the decanoate. Approximately 80% of the administered esters were converted to fluphenazine or its major metabolite, 7-hydroxyfluphenazine.

TOXICOLOGY

Acute Toxicity

TABLE 1.
Median lethal dose of fluphenazine
in mice and rats.

Animal	Route of Administration	ED_{50} in mg/kg ± S.E. Fluphenazine
Mouse	Intravenous	51 ± 4.6 (n=50)
	Intraperitoneal	89 ± 7.9 (n=20)
	Oral	220 ± 17.2 (n=30)
Rat	Intraperitoneal	100 ± 19.2 (n=50)

Subacute and Chronic Toxicity

Studies in rats and dogs are summarized in Table 2.

TABLE 2.
Subacute and chronic toxicity.

	Rats	Dogs
Type of study	Subcute	Subcute
Route	Subcutaneous	Subcutaneous
Duration	3 months	3 months
Dosage	0, 3, 10, 30 mg/kg/wk	0, 10, 30, 90 mg/kg/wk stepped up to 10.0 mg/kg
Growth, food and water consumption	Marketed reduction in weight gain in level males; moderate loss in weight gain in other test animals. Growth retardation associated with reduction in food and water consumption.	No drug related effect seen
Behaviour, drug-related effects	Depression proportional to dosage.	Moderate reduction in activity, miosis, prolapsed nictitating memorane, muscle tremors.
Mortality & morbundity	None	None
Hematology	Normal	Normal except one high dose dog with reduction in neutophils
Clinical chemistries	Normal	Mostly normal
Urine	Negative	No drug-related effects
Organ weights	No drug-related effects	No drug-related effects
Pathology	No drug-related effects	No prophological evidence of toxicity.

Groups of 24 rats (12M + 12F) were dosed subcutaneously with 0, 3, 10 and 30 mg/kg body weight/week of fluphenazine decanoate in sesame oil vehicle for 3 months. Growth retardation associated with reduction in food and water consumption was seen. Depression, proportional to dosage and seen even 7 weeks post-dosage, was observed in rats on all three levels. No ocular changes were seen.

Groups of four dogs were given 0, 10, 30 and 90 mg/kg/week fluphenazine decanoate subcutaneously as 2.5% solution in sesame oil over 3 months. All dogs in the 90 mg/kg group and some in the 30 mg/kg and 10 mg/kg groups exhibited one or more of the following effects: decrease in activity, miosis, prolapsed nictitating membrane and muscle tremors. After the tenth week, only the 90 mg/kg dogs showed these effects. Hematology was normal except for a moderate reduction in neutrophils in one high dosage group dog. Clinical chemistries were normal but BSPs were elevated in one high dosage group, two intermediate dosage group, one low dosage group and one control group dog.

Results of these studies indicated a low order of toxicity in the test animals. The effects seen with fluphenazine decanoate were very similar to those seen with the dihydrochloride and enanthate esters.

Reproduction and teratology

Groups of adult female rabbits were mated and given a single subcutaneous injection of fluphenazine decanoate at one of the following doses: 0, 0.84 and 5.6 mg/kg on the sixth day after mating.

All rabbits in the control and low dose groups survived; 10/15 rabbits/group became pregnant. In the high dose group, 11/19 animals were characterized as being pregnant but in 3/11, no in utero implant sites were observed. The failure to observe implant sites in 3 animals indicating hemorrhagic corpora lutea at the high dosage levels suggests a possible interference with nidation in these rabbits.

The mean numbers of implant sites, live fetuses/litter at termination, dead fetuses/litter, weights of the live fetuses, were similar in all groups. Gross examination at autopsy revealed no adverse findings in about one third of the pups. A delay in ossification characterized by a lack of closure in the coronal suture between the parietal and frontal bones was seen in 58% of the high dose fetuses.

Muscle irritation study

A single 0.25 mL of fluphenazine decanoate was injected into the vastus lateralis muscle of 4 rabbits. Two rabbits were sacrificed after 2 days and two, after 7 days. The injected muscles were excised and examined grossly for local irritation.

After 2 days of the injection, very mild irritation, consisting of a slight diffuse hemorrhage and slight degeneration, was seen. Only a small amount of fibrosis was observed on day 7.

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