Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams.
Autonomic Nervous System
Hypertension and fluctuations in blood pressure have been reported with fluphenazine
Hypotension has rarely presented a problem with fluphenazine. However, patients with pheochromocytoma, cerebral, vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. If severe hypotension should occur, supportive measures including the use of intravenous vasopressor drugs should be instituted immediately. Norepinephrine Bitartrate Injection is the most suitable drug for this purpose: epinephrine should not be used since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.
Autonomic reactions including nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Autonomic effects can usually be controlled by reducing or temporarily discontinuing dosage. In some patients, phenothiazine derivatives have caused blurred vision, glaucoma, bladder paralysis, fecal impaction paralytic ileus, tachycardia, or nasal congestion.
Metabolic and Endocrine
Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have all been known to occur in some patients on phenothiazine therapy.

Allergic Reactions
Skin disorders such as itching, erythema, urticaria, seb orrhea, photosensitivity, eczema and even exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.
Hematologic
Routine blood counts are advisable during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, 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.
Hepatic
Liver damage as manifested by cholestatic jaundice may be discontinued if this occurs.
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. Several patients have shown sudden flareups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.
Although this is not a general feature of fluphenazine, potentiation of CNS depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur. The following adverse reactions have also occurred with phenothiazine derivatives: Systemic lupus erythematosuslike syndrome, hypotension severe enough to cause fatal cardiac arrest, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long term use, skin pigmentation, and lenticular and corneal opacities.
Injections of fluphenazine decanoate are extremely well tolerated, local tissue reactions occurring only rarely.

13. Overdosage and treatment
Overdosage should be treated symptomatically and supportively, extrapyramidal reactions will respond to oral or parenteral anti-parkinsonian drugs such as procyclidine or benzatropine. In cases of severe hypotension, all procedures for the management of circulatory shock should be instituted, eg vasoconstrictors and/or intravenous fluids. However, only the vasoconstrictors metaraminol or noradrenaline should be used, as adrenaline may further lower the blood pressure through interaction with the phenothiazine.

14. Storage Condition
Store at temperatures not exceeding 30°C. Protect from light.

15. Dosage forms and packaging available
1mL Type 1 amber glass ampoule (Box of 5's)

16. CAUTION
Foods, Drugs, Devices and Cosmetic Act prohibits dispensing without prescription.

17. ADR STATEMENT For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

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19. Manufactured by:
Pharmafabrikon
91-1 Sivagangai Road, Vilathur, Madurai 625-020, India
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Belkam Philippines, Inc.
Unit 2303, Cityland Herrera Tower, 98 V.A. Rufino St., cor. Valero St.
Salcedo Village, Makati City
Distributed by:
B & M Pharma Trading Co.
#9 Rizal Ave., San Isidro, Taytay Rizal

Fluphenazine decanoate

℞

Fludexin

25 mg/mL
Solution for Injection (IM)

1. Product Name - Fluphenazine decanoate

2. Formulation:
Each ampoule contains:
Fluphenazine decanoate…..... 25 mg

3. Product Description – A yellow colored oil liquid for intramuscular IM Injection providing 25 mg Fluphenazine decanoate per mL in sesame oil as vehicle and benzyl alcohol as preservative contained in an amber coloured ampoule.

4. Pharmacodynamics and Pharmacokinetics
Fluphenazine decanoate is very slowly absorbed from the site of intramuscular injection. Fluphenazine is gradually released into the body and are therefore suitable for use as depot injections. The plasma half-life of fluphenazine decanoate has been reported to be 6 to 9 days after intramuscular injection.
Absorption:
Rapidly absorbed from GI tract and from parenteral sites. Peak serum concentrations were attained within 1.5 – 2 or 0.5 hours after intramuscular (IM) or oral administration, respectively of Fluphenazine.
Distribution:
Not fully elucidated; reportedly crosses blood-brain barrier. Phenothiazines cross the placenta and are distributed into milk.
Metabolism:
Metabolic fate not fully elucidated.
Elimination:
Excreted in feces and urine as unchanged drug, Fluphenazine sulfoxide, and 7-hydroxyfluphenazine following IM administration of Fluphenazine Decanoate in 1 patient studied, also excreted in urine as metabolite conjugates.

5. Indication
Fluphenazine is used in the treatment of psychiatric disorders including schizophrenia, mania, severe anxiety and behavioral disturbances.
Fluphenazine decanoate has not been shown effective in the management of behavioral complications in patients with mental retardation.

6. Recommended Dose
Adults:
It is recommended that patients be stabilized on the injection in hospital.
Recommended dosage regimes for all indications:
A. Patients without previous exposure to a depot fluphenazine formulation:
Initially 0.5 mL ie. 12.5 mg (0.25 mL ie. 6.25 mg for patients over 60) by deep intramuscular injection into the gluteal region.
The onset of action generally appears between 24 and 72 hours after injection and the effects of the drug on psychotic symptoms become significant within 48 to 96 hours. Subsequent injections and the dosage interval are determined in accordance with the patient's response. When administered as maintenance therapy, a single injection may be effective in controlling schizophrenic symptoms for up to four weeks or longer.
It is desirable to maintain as much flexibility in the dose as possible to achieve the best therapeutic response with the least side-effects; most patients are successfully maintained within the dose range 0.5 mL (12.5 mg) to 4 mL (100 mg) given at a dose interval of 2 to 5 weeks.
Patients previously maintained on oral fluphenazine;
It is not possible to predict the equivalent dose of depot formulation in view of the wide variability of individual response.
B. Patients previously maintained on depot fluphenazine;
Patients who have suffered a relapse following cessation of depot fluphenazine therapy may be restarted on the same dose, although the frequency of injections may need to be increased in the early weeks of treatment until satisfactory control is obtained.
Elderly:
Elderly patients may be particularly susceptible to extrapyramidal reactions, sedative and hypotensive effects. In order to avoid this, a reduced maintenance dosage may be required and a smaller initial dose.
Children:
Not recommended for children.
*Where a smaller volume of injection is desirable, patients may be transferred directly to the equivalent dose of Fluphenazine Decanoate Injection on the basis that 1ml Fluphenazine Concentrate Injection is equivalent to 4 mL Fluphenazine Decanoate Injection.

Note: The dosage should not be increased without close supervision and it should be noted that there is a variability in individual response.
The response to antipsychotic drug treatment may become apparent for several weeks or months.

7. Mode of Administration: Intramuscularly

8. Contraindication
Fluphenazine is contraindicated in patients with suspected or established subcortical brain damage, in patients receiving large doses of hypnotics, and in comatose or severely depressed states. The presence of blood dyscrasias or liver damage. Know hypersensitivity to fluphenazine or other phenothiazines derivatives (unless potential benefits outweigh possible risks).
Fluphenazine Solution for Injection is contraindicated in the following cases
Comatose states
Marked cerebral atherosclerosis

Phaeochromocytoma
Renal failure
Liver failure
Severe cardiac insufficiency
Severely depressed states
Existing blood dyscrasias
Hypersensitivity to Fluphenazine Decanoate or to any of the excipients

9. Warnings and Precautions for Use

WARNINGS: The use of Benzyl Alcohol should be avoided in children under two years of age. Not to be used at all in neonates, particularly in the premature.

Caution should be exercised with the following:
Liver disease
Renal impairment
Cardiac arrhythmias, cardiac disease
Thyrotoxicosis
Severe respiratory disease
Epilepsy, conditions predisposing to epilepsy (eg. alcohol withdrawal or brain damage)
Parkinson's disease
Patients who have shown hypersensitivity to other phenothiazines
Personal or family history of narrow angle glaucoma In very hot weather
The elderly, particularly if frail or at risk of hypothermia
Hypothyroidism
Myasthenia gravis
Prostatic hypertrophy

Patients with known or with a family history of cardiovascular disease should receive ECG screening, and monitoring and correction of electrolyte balance prior to treatment with fluphenazine.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with fluphenazine and preventative measures undertaken.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Psychotic patients on large doses of phenothiazines who are undergoing surgery should be watched carefully for hypotension. Reduced amounts of anaesthetics or central nervous system depressants may be necessary.

Fluphenazine should be used with caution in patients exposed to organophosphorus insecticide.

As with any phenothiazine, the physician should be alerted to the possibility "silent pneumonias" in patients receiving long-term fluphenazine.

Fluphenazine is not licensed for the treatment of dementia-related behavioural disturbances.

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with fatal "Gasping Syndrome" (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse). As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy.

10. Interaction with other medicinal products and other forms of interactions

The possibility should be borne in mind that phenothiazines may:

- Increase the central nervous system depression produced by drugs such as alcohol, general anaesthetics, hypnotics, sedatives or strong analgesics.
- Antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood-pressure lowering effects of adrenergic-blocking agents such as guanethidine and clonidine.
- Impair: the anti-parkinsonian effect of L-dopa; the effect of anti-convulsants; metabolism of tricyclic antidepressants; the control of diabetes.
- Increase the effect of anticoagulants and antidepressants.
- Interact with lithium.

Anticholinergic effects may be enhanced by anti-parkinsonian or other anticholinergic drugs.

Phenothiazines may enhance; the absorption of corticosteroids, digoxin, and neuromuscular blocking agents.

Fluphenazine is metabolised by P450 2D6 and is itself an inhibitor of this drug metabolising enzyme. The plasma concentrations and the effects of fluphenazine may therefore be increased and prolonged by drugs that are either the substrates or inhibitors of this P450 isoform, possibly resulting in severe hypotension, cardiac arrhythmias or CNS side effects. Examples of drugs which are substrates or inhibitors of cytochrome P450 2D6 include anti-arrhythmics, certain antidepressants including SSRIs and tricyclics, certain antipsychotics, B-blockers, protease inhibitors, opiates, cimetidine and ecstasy (MDMA). This list is not exhaustive.

Concomitant use of barbiturates with phenothiazines may result in reduced serum levels of both drugs, and an increased response if one of the drugs is withdrawn.

The effect of fluphenazine on the QT interval is likely to be potentiated by concurrent use of other drugs that also prolong the QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Examples include certain anti-arrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol), tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as phenothiazines and pimozide);

certain antihistamines (such as terfenadine); lithium, quinine, pentamidine and sparfloxacin.

Electrolyte imbalance, particularly hypokalaemia, greatly increases the risk of QT interval prolongation. Therefore, concurrent use of drugs that cause electrolyte imbalance should be avoided.

Concurrent use of MAO inhibitors may increase sedation, constipation, dry mouth and hypotension.

Owing to their adrenolytic action, phenothiazines may reduce the pressor effect of adrenergic vasoconstrictors (i.e. ephedrine, phenylephrine).

Phenylpropanolamine has been reported to interact with phenothiazines and cause ventricular arrhythmias.

Concurrent use of phenothiazines and ACE inhibitors or angiotensin II antagonists may result in severe postural hypotension.

Concurrent use of thiazide diuretics may cause hypotension. Diuretic-induced hypokalaemia may potentiate phenothiazine-induced cardiotoxicity.

Clonidine may decrease the antipsychotic activity of phenothiazines,

Methyldopa increases the risk of extrapyramidal side effects with phenothiazines.

The hypotensive effect of calcium channel blockers is enhanced by concurrent use of antipsychotic drugs.

Phenothiazines may predispose to metrizamide-induced seizures.

Concurrent use of phenothiazines and cocaine may increase the risk of acute dystonia.

There have been rare reports of acute Parkinsonism when an SSRI has been used in combination with a phenothiazine.

Phenothiazines may impair the action of anti-convulsants. Serum levels of phenytoin may be increased or decreased.

Phenothiazines inhibit glucose uptake into cells, and hence may affect the interpretation of PET studies using labelled glucose.

11. Pregnancy and Lactation

Pregnancy

Fluphenazine Decanoate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The safety for the use of this drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential benefits when administering this drug to pregnant patients.

Non-teratogenic Effects

Neonates exposed to psychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Nursing mothers; Breast feeding is not recommended during treatment with depot fluphenazines, owing to the possibility that fluphenazine is excreted in the breast milk.

12. Undesirable effects

Fluphenazine is less likely to cause sedation, hypotension, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects.

Central Nervous System

The side effects most frequently reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied byhyperthermia has been reported following use of fluphenazine decanoate. Most often these extrapyramidal symptoms are reversible; however, they may be persistent (see below). The frequency of such reactions is related in part to chemical structure; one can expect a higher incidence with fluphenazine decanoate than with less potent piperazine derivatives or with straight chain phenothiazines such as chlorpromazine. With any given phenothiazine derivative, the incidence and severity of such reactions depend more on individual patient sensitivity than on other factors, but dosage level and patient age are also determinants. Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions can usually be controlled by administration of antiparkinsonian drugs such as Benztropine Mesylate or Intravenous Caffeine ad Sodium Benzoate Injection, and by subsequent reduction in dosage.

Tardive Dyskinesia

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely. The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatments. Early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of the neuroleptic drug should be reduced periodically 9if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, since neuroleptic drugs may mask the signs of the syndrome.

Other CNS Effects

Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy, leukocytosis, elevated CPK, liber function abnormalities, and acute renal failure may also occur with NMS. Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induction of a catatonic like state has been known to occur with dosages of fluphenazine far in excess of the recommended amounts. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered.