PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr FLUPHENAZINE

Fluphenazine Hydrochloride Tablets

Tablets, 1 mg, 2 mg, and 5 mg, oral

USP

Antipsychotic

AA PHARMA INC

Vaughan, Ontario

L4K 4N7

www.aapharma.ca

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RECENT MAJOR LABEL CHANGES

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3 Serious Warnings and Precautions Box	05/2022
4 Dosage and Administration, 4.1 Dosing Considerations	05/2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUPHENAZINE (fluphenazine hydrochloride) is indicated for:

- Management of manifestations of psychotic disorders.
- Treatment of behavioral disorders in adults.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLUPHENAZINE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics and 8 ADVERSE REACTIONS.

1.2 Geriatrics

Geriatrics (>60 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

Fluphenazine is contraindicated in:

- Patients who are hypersensitive to fluphenazine or cross sensitivity to other phenothiazines or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Comatose or depressed states due to CNS depressants, alcohol; blood dyscrasias, bone marrow depression, liver damage.
- Patients with suspected or established subcortical brain damage with or without hypothalmic damage, since a hyperthermic reaction with temperatures in excess of 40°C may occur in such patient, sometimes not until 14 to 16 hours after drug administration. Total body ice packing is recommended for such a reaction; antipyretics may also be useful.
- Patients receiving large doses of hypnotics due to the possibility of potentiation.
- Patients with pheochromocytoma, cerebrovascular or renal insufficiency, or severe cardiac reserve deficiency such as mitral insufficiency, as well as patients who have exhibited idiosyncrasy to other centrally-acting drugs may experience severe reactions to phenothiazine compounds and are particularly prone to hypotensive reactions.
- Patients who will receive spinal or general anesthesia.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia

Elderly patients with dementia treated with antipsychotic drugs are at an increased risk of death compared to those treated with placebo (see 7.1.4 Geriatrics). FLUPHENAZINE is not approved for use in elderly patients with dementia.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients should have baseline and periodic monitoring of blood glucose and body weight.

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. It is recommended that patients have their complete blood count (CBC), WBC, differential counts and liver function tests prior to starting FLUPHENAZINE and then periodically throughout treatment.

All potential risk factors for venous thromboembolism (VTE) should be identified and preventative measures undertaken when prescribing FLUPHENAZINE.

4.2 Recommended Dose and Dosage Adjustment

Initial Dose

Mental disorders and behavioral problems: depending on severity and duration of symptoms, the daily dosage for psychotic patients may range initially from 2.5 to 10 mg in divided doses given at 6 to 8 hour intervals.

The smallest amount that will produce the desired results must be carefully determined for each individual, since the optimal dosage varies from patient to patient.

Treatment is best instituted with the initial dosage, which may be increased, if necessary, until the desired clinical effects are achieved.

Maximum Dose

Daily dosages exceeding 20 mg should be used with caution.

Maintenance Dose

When symptoms are controlled, dosage can generally be reduced gradually to daily maintenance doses of 1 to 5 mg, often given as a single daily dose. Continued treatment is needed to achieve maximum therapeutic benefits; further adjustments in dosage may be necessary during the course of therapy to meet the patient's requirements.

Dosing Considerations in Special Populations

Patients ≥60 years of age: The suggested starting dose is 1 to 2.5 mg daily, adjusted according to the response of the patient.

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Renal impairment: Treatment with FLUPHENAZINE is contraindicated in patients with renal insufficiency (see 2 CONTRAINDICATIONS).

Hepatic impairment: Patients with hepatic impairment should receive FLUPHENAZINE with caution (see 2 CONTRAINDICATIONS).

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Symptoms: Overdosage is usually signified by parkinsonism, hypotension and sedation.

Treatment: Essentially supportive and symptomatic; the drug should be discontinued or the dosage reduced, and in severe cases, vomiting should be induced or gastric lavage should be instituted if the patient is conscious. Maintain the airway by any means necessary. Hypotension calls for the immediate use of an i.v. vasopressor drug such as levarterenol bitartrate USP. Epinephrine should not be used, as a further lowering of blood pressure may result. Symptoms of parkinsonism may be treated with such agents as benztropine mesylate of diphenhydramine HCl. CNS symptoms of anticholinergic type toxic effects can be reversed by physostigmine salicylate.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 1 mg, 2 mg, 5 mg of fluphenazine hydrochloride	carnauba wax, cornstarch, D&C red #30 aluminum lake 30% (2 mg only), erythrosine lake 40% (1 mg only), hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

FLUPHENAZINE (fluphenazine hydrochloride) 1 mg tablet: Each bright pink, round, biconvex, film-coated tablet, engraved "1" on one side, other side plain, contains 1 mg fluphenazine hydrochloride. Available in bottles of 100 tablets.

FLUPHENAZINE (fluphenazine hydrochloride) 2 mg tablet: Each pink, round, biconvex, film-coated tablet, engraved "2" on one side, other side plain, contains 2 mg fluphenazine hydrochloride. Available in bottles of 100 tablets.

FLUPHENAZINE (fluphenazine hydrochloride) 5 mg tablet: Each white, round, biconvex, film-coated tablet, engraved "5" on one side, other side plain, contains 5 mg fluphenazine hydrochloride. Available in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

FLUPHENAZINE may increase the effects of general anesthetics, opiates, barbiturates, alcohol and other CNS depressants as well as atropine and phosphorus insecticides. (See 9.4 Drug-Drug Interactions)

The antiemetic effect of FLUPHENAZINE can obscure signs of toxicity due to overdosage of other drugs, or mask the symptoms of disease.

Use with caution in patients exposed to extreme heat.

Cardiovascular

Hypotension: Hypotension, which is typically orthostatic, may occur especially in elderly and in alcoholic patients. This effect may be additive with other hypotensive agents. Exercise special care in those patients in whom a hypotensive crisis would be undesirable, such as those with arteriosclerosis or other cardiovascular diseases.

QT Interval: Prolongation of the QT interval, flattening and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving phenothiazines. These changes appear to be reversible and related to a disturbance in repolarization. Give phenothiazines cautiously to patients with heart disease.

Anginal Pain: The occasional increase in physical activity resulting from FLUPHENAZINE administration may augment the severity of anginal pain. Observe affected patients carefully and withdraw the drug if necessary.

Dependence/Tolerance

In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea, vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy.

Driving and Operating Machinery

Where patients are participating in activities requiring complete mental alertness, such as driving an automobile or operating machinery, administer the phenothiazine cautiously, forewarn the patient, and increase the dosage gradually.

Endocrine and Metabolism

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Gastrointestinal

Use with caution in patients with a history of ulcer disease.

Paralytic ileus, even resulting in death, may occur, especially in the elderly. This possibility should be kept in mind and appropriate measures should be taken if constipation develops.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as FLUPHENAZINE. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Most reported cases of agranulocytosis associated with the administration of phenothiazine derivatives have occurred between the fourth and tenth week of treatment. Therefore, observe patients on prolonged therapy with particular care during that time for the appearance of such signs as sore throat, fever and weakness. If these symptoms appear, discontinue the drug and perform liver function tests. It is also advisable to perform WBC and differential counts and liver function tests periodically during therapy.

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting FLUPHENAZINE and then periodically throughout treatment.

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including FLUPHENAZINE, in case reports and/or observational studies. When prescribing FLUPHENAZINE all potential risk factors for VTE should be identified and preventative measures undertaken.

Monitoring and Laboratory Tests

- Blood glucose and body weight at baseline and periodically throughout treatment.
- Complete blood count (CBC) at baseline and periodically throughout treatment.
- WBC and differential counts and liver function tests periodically during therapy
- Sore throat, fever and weakness in patients on prolonged therapy may indicate agranulocytosis. If these symptoms appear, discontinue the drug and perform liver function tests.
- Renal function of patients on prolonged therapy. If abnormal values are observed, discontinue the drug.

Neurologic

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia: (See also 8.1 Adverse Reaction Overview, Tardive Dyskinesia). A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although the prevalence of tardive dyskinesia with conventional antipsychotics appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the beginning of treatment, which patients are likely to develop the syndrome.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible

are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn.

Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of tardive dyskinesia and thereby may possibly mask the underlying process.

The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given this consideration, Fluphenazine should be prescribed in a manner that is most likely to minimize the risk of the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic Fluphenazine use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on Fluphenazine, drug discontinuation should be considered. However, some patients may require treatment with Fluphenazine despite the presence of the syndrome.

Seizures: Use FLUPHENAZINE cautiously in patients with a history of seizures since grand mal convulsions have been known to occur.

Ophthalmologic

Phenothiazines have been associated with retinopathy and lenticular or corneal deposits. Discontinue FLUPHENAZINE if retinal changes are observed.

Peri-Operative Considerations

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or CNS depressants may be required.

Renal

Monitor the renal function of patients on long-term therapy since elevation of BUN has been reported. If abnormal values are observed, discontinue the drug. Patients who may develop urinary retention should be carefully observed. This drug should not be used in patients with renal insufficiency (see 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

  Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs (including FLUPHENAZINE) 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.

7.1 Special Populations

7.1.1 Pregnant Women

FLUPHENAZINE should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Safe use of FLUPHENAZINE in pregnancy has not been established. Therefore, it should not be administered to women of childbearing potential, particularly during the first trimester of pregnancy, unless the expected benefit to the patient outweighs the potential risk to the fetus.

7.1.2 Breast-feeding

Use of FLUPHENAZINE during breast-feeding should be avoided.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of FLUPHENAZINE in pediatric patients have not been established, as there has been inadequate experience with the drug in this age group, therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Patients ≥60 years of age: Paralytic ileus, even resulting in death, may occur, appropriate measures should be taken if constipation develops.

Use in Geriatrics with Dementia

Overall Mortality

FLUPHENAZINE is not indicated for the treatment of elderly patients with dementia.

In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with atypical antipsychotic drugs had an increased risk of mortality compared to placebo.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects with different phenothiazines vary in type, frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

In general, members of the piperazine group of phenothiazines have more marked stimulating effects, are more likely to cause motor disorders associated with extrapyramidal reactions, particularly in children, but are less likely to cause blood dyscrasias, hypotension, tachycardia, and drowsiness than the members of the other phenothiazine groups.

Not all of the following adverse reactions have been reported with every phenothiazine derivative, but they have been reported with one or more, and should be borne in mind when drugs of this class are administered.

Behavioral Reactions: oversedation; impaired psychomotor function; paradoxical effects, such as agitation, excitement, insomnia, bizarre dreams, aggravation of psychotic symptoms; toxic confusional states.

CNS Effects: extrapyramidal reactions, including pseudoparkinsonism (with motor retardation, rigidity, mask- like facies, pill rolling and other tremors, drooling, shuffling gait); dystonic reactions (including perioral spasms, and trismus, tics, torticollis, oculogyric crises, protrusion of the tongue, difficulty swallowing, carpopedal spasm and opisthotonas of the back muscles); and akathisia. Persistent dyskinesias resistant to treatment have been reported, particularly in elderly patients with previous brain damage. In addition, altered EEG tracings, disturbed body temperature and lowering of the convulsive threshold have occurred. Dizziness has been reported.

Tardive Dyskinesia: May appear in some patients on long-term antipsychotic therapy, or may appear after drug therapy has been discontinued. The risk appears 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 extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of the syndrome. All antipsychotic agents should 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 neuroleptics and reducing the dose or discontinuing the drug, if possible, when manifestations of the syndrome are recognized, particularly in patients over the

age of 50. Fine vermicular movements of the tongue may be an early sign of the syndrome. If the medication is stopped at that time, the syndrome may not develop.

Autonomic Nervous System: dry mouth, fainting, stuffy nose, photophobia, blurred vision, miosis, hypertension, hypotension (see 7 WARNINGS AND PRECAUTIONS) salivation, perspiration, headache.

Gastrointestinal Effects: anorexia, increased appetite, gastric irritation, nausea, vomiting, constipation, paralytic ileus.

Endocrine Effects: altered libido, menstrual irregularities, lactation, false positive pregnancy tests, inhibition of ejaculation, gynecomastia, weight gain.

Dermatological Effects: itching rash, hypertrophic papillae of the tongue, angioneurotic edema, erythema, allergic purpura, exfoliative dermatitis, contact dermatitis.

Cardiovascular Effects: hypotension, tachycardia, ECG changes. See 7 WARNINGS AND PRECAUTIONS.

Blood Dyscrasias: agranulocytosis, leukopenia, granulocytopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: jaundice, biliary stasis.

Urinary Disturbances: retention, incontinence.

Abnormal Pigmentation: Recently, a peculiar skin eye syndrome has been recognized as an adverse effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of skin or conjunctiva and/or discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Patients receiving higher doses of phenothiazines for prolonged periods should have periodic complete eye examinations.

Miscellaneous: 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 flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions. The physician should therefore be alert to the possible development of "silent pneumonias".

The following have also occurred with the phenothiazines: systemic lupus erythematosus like syndrome, altered CSF proteins, cerebral edema.

Patients should be advised of the risk of severe constipation during FLUPHENAZINE treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
General anesthetics, opiates, barbiturates, alcohol, other CNS depressants.	T	Phenothiazines may increase the effects of general anesthetics, opiates, barbiturates, alcohol and other CNS depressants.	Dosage adjustment may be necessary.
Atropine	T	Phenothiazines may increase the effects of atropine	Dosage adjustment may be necessary.
Phosphorus insecticides	T	Phenothiazines may increase the effects of phosphorus insecticides	Dosage adjustment may be necessary.
Epinephrine	T	Phenothiazines may reverse epinephrine's action and thereby cause a further fall in blood pressure.	Avoid epinephrine in the treatment of phenothiazine induced hypotension.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Phenothiazine derivatives appear to act on the hypothalamus, depressing various components of the mesodiencephalic activating system which is involved in the control of basal metabolism and body temperature, wakefulness, vasomotor tone, emesis and hormonal balance. In addition, the drugs exert a peripheral autonomic effect in varying degrees. However, the site and mode of action of the phenothiazine derivatives have not been completely elucidated.

10.2 Pharmacodynamics

In the treatment of psychotic disorders, FLUPHENAZINE, like other phenothiazine derivatives, alleviates many of the psychotic symptoms, although it does not substantially alter the basic psychotic process. The drug is primarily effective in reducing hostility, anxiety, agitation and hyperactivity; confusion, hallucinations and delusions are affected to a lesser degree. In general, the psychotic patient becomes more cooperative, more responsive to social situations, and more subject to basic therapy.

10.3 Pharmacokinetics

Information is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15 to 30°C. Keep container tightly closed. Protect from light.

FLUPHENAZINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

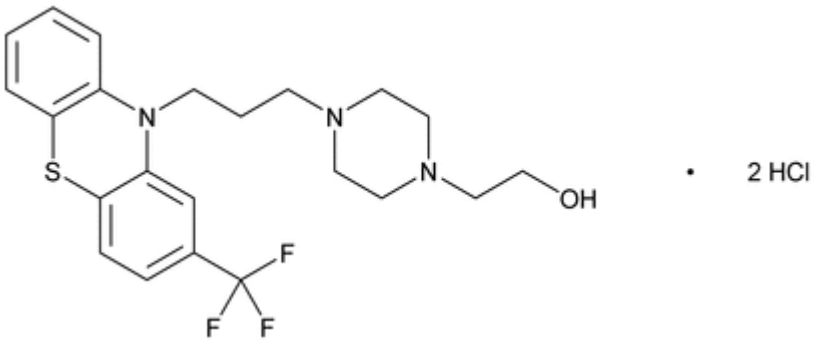
12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Fluphenazine hydrochloride
Chemical name:	• 2-[4-[3-[2-(Trifluoromethyl)-10H-phenothiazin-10-yl]-propyl]piperazin-1-yl]ethanol dihydrochloride
Molecular formula and molecular mass:	$C_{22}H_{26}F_3N_3OS$. 2 HCl and 510.44 g/mol
Structural formula:	 • 2 HCl
Physicochemical properties:	A white or almost white crystalline powder. It is freely soluble in water, sparingly soluble in ethanol, very slightly soluble in acetone, very slightly soluble in chloroform, practically insoluble in benzene and ether. pKa as follows pKa1 = 3.65, pKa2 = 5.95, pKa3 = 7.93.
Pharmaceutical standard:	USP

Product Characteristics:

In addition to the active ingredient, fluphenazine hydrochloride, each tablet also contains the non-medicinal ingredients: carnauba wax, cornstarch, D&C red #30 aluminum lake 30% (2 mg only), erythrosine lake 40% (1 mg only), hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Information is not available.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]FLUPHENAZINE

Fluphenazine Hydrochloride Tablets

Read this carefully before you start taking **FLUPHENAZINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLUPHENAZINE**.

Serious Warnings and Precautions

Elderly Patients with Dementia: There is an increased risk of death when antipsychotic medications, such as FLUPHENAZINE, are used in elderly patients with dementia. FLUPHENAZINE is **not** to be used if you are older than 60 years of age and have dementia.

What is FLUPHENAZINE used for?

FLUPHENAZINE is used in adults to manage the symptoms of mental health conditions. FLUPHENAZINE can also be used in adults to treat behavioural disorders.

How does FLUPHENAZINE work?

FLUPHENAZINE belongs to a class of medicines known as antipsychotics. The exact way FLUPHENAZINE works is not known. However, it is thought to re-adjust the balance of certain chemicals in the brain (i.e., dopamine and serotonin) that allow communication between nerve cells.

What are the ingredients in FLUPHENAZINE?

Medicinal ingredient: Fluphenazine hydrochloride.

Non-medicinal ingredients: Carnauba wax, cornstarch, D&C red # 30 aluminum lake 30% (2 mg only), erythrosine lake 40% (1 mg only), hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

FLUPHENAZINE comes in the following dosage forms:

Tablets: 1 mg, 2 mg, and 5 mg of fluphenazine hydrochloride.

Do not use FLUPHENAZINE if:

- you are allergic to fluphenazine or any other ingredients in FLUPHENAZINE.
- you are allergic to other phenothiazines. If you are unsure, ask your healthcare professional.
- you have a medical condition known as pheochromocytoma (a tumor of the adrenal gland).
- you have severe heart or blood vessel problems.
- you have kidney problems.
- you have or have had brain damage.
- you have decreased alertness, drowsiness, slow breathing, or a weak pulse. This can include if:
    - you are taking certain medicines known as central nervous system (CNS) depressants. If you are unsure, ask your healthcare professional;
    - you have consumed alcohol;
    - you have blood cell disorders (e.g., low white blood cell counts or low platelet counts);
    - you have bone marrow problems;
    - you have liver problems.
- you are receiving or plan to receive anesthesia (medicines used to induce sleep and prevent pain during surgery).
- you are taking hypnotics (medicines used to help with sleep).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUPHENAZINE. Talk about any health conditions or problems you may have, including if you:

- have heart or blood vessel problems.
- have an eye condition known as glaucoma.
- have prostate problems (enlarged prostate gland in men).
- are addicted to alcohol or have problems with alcohol. You should not take FLUPHENAZINE if you are under the effects of alcohol.
- are pregnant or planning to become pregnant. FLUPHENAZINE should not be used during pregnancy unless your healthcare professional considers the benefits to you markedly outweigh the potential risks to the fetus.
- have or ever had a blackout or seizure.
- are breast feeding or planning to breast feed.
- have or ever had ulcers.
- are at a higher risk of developing blood clots. This can include if you:
    - have family history of blood clots,
    - are over 65 years old,
    - smoke,

    - are considered obese,
    - recently had a major surgery (such as hip or knee replacement),
    - are immobile (prolonged inactivity) due to air travel or other reason, or
    - take oral contraceptives ("The Pill").
- are exposed or will be exposed to extreme heat. Avoid exposure to extreme heat.
- have difficulties urinating.
- have problems with low sex hormone levels.

Other warnings you should know about:

Driving and using machines: FLUPHENAZINE may affect your mental and physical abilities. This may be more likely to occur when you start your treatment and when your dose is increased. Before you drive or do tasks that require special attention, wait until you know how you respond to FLUPHENAZINE. You should be cautious when driving a car or operating machinery.

Testing and check-ups: Your healthcare professional will monitor your health throughout your treatment. They may do this by performing certain tests before and periodically during your treatment. This will tell your healthcare professional how FLUPHENAZINE is affecting you. These tests may monitor:

- your blood glucose level;
- your body weight;
- the profile of your blood (e.g., red blood cell, white blood cell, and platelet counts);
- your liver and kidney function; and
- your eyes.

Pregnancy: You should not take FLUPHENAZINE while you are pregnant or if you are planning on becoming pregnant unless you have talked to your healthcare professional about it. If you took FLUPHENAZINE at any time while you were pregnant or if you took it before you became pregnant, the following symptoms may happen in your newborn baby:

- shaking,
- stiffness in their muscles and/or weakness,
- sleepiness,
- agitation,
- breathing problems, or
- difficulty feeding.

Get medical help right away if your newborn has any of these symptoms.

Taking FLUPHENAZINE may also affect your pregnancy tests by producing false-positive pregnancy results.

Hyperprolactinemia (increased levels of prolactin): FLUPHENAZINE can raise your levels of a hormone called "prolactin". This is measured with a blood test. Symptoms may include:

- In men:
  - swelling in the breast,
  - difficulty in getting or maintaining an erection or other sexual dysfunction.
- In women:
  - discomfort in the breasts,
  - leaking of milk from the breasts (even if not pregnant),
  - missing your menstrual period or other problems with your cycle.

If you have high levels of prolactin and a condition called hypogonadism, you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLUPHENAZINE:

- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - alcohol. FLUPHENAZINE can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on FLUPHENAZINE therapy.
  - general anesthetics, medicines used during surgery.
  - barbiturates, medicines used to relax the body and help with sleeping.
  - opiates, medicines used to relieve pain (e.g., codeine).
  - muscle relaxants, medicines used to treat muscle spasms and back pain (e.g., suxamethonium, pancuronium and dantrolene).
  - antianxiety agents, medicines used to reduce anxiety.
  - sedatives, medicines used to help with sleep.
  - antihistamines, medicines used to treat allergies and may cause drowsiness (e.g., diphenhydramine).
  - cisapride, a medicine used to treat gastric reflux (the regurgitation of stomach acid into the esophagus).
  - cabergoline, a medicine used to treat high levels of prolactin hormone in your body.
  - antiepileptics, medicines used to control seizures or fits.
  - medicines that may make you sleepy or drowsy (e.g., cough-and-cold medicines and sleeping pills). You should not take FLUPHENAZINE if you have drowsiness caused by other medicines.
- antidepressants, medicines used to treat depression.
- atropine, a medicine that can be used to treat symptoms of low heart rate, irritable bowel syndrome, asthma, or incontinence.

- phosphorus insecticides used for farming, treating animals (e.g., flea and tick control), and treating pests around the house or garden. FLUPHENAZINE can increase the toxicity from these types of insecticides, so caution must be taken when using these products.
- hypotensive agents, medicines that are used for low blood pressure (e.g., epinephrine).
- antibiotics, medicines used to treat bacterial infections (e.g., grepafloxacin and sparfloxacin).
- lithium, a medicine used to treat mood disorders.
- metrizamide, a radiocontrast agent used to improve the contrast of internal body structures using different imaging techniques such as computed tomography scans (CT) or radiography (X-ray imaging).
- antihypertensive agents, medicines used for high blood pressure (e.g., guanethidine and guanadrel).
- St. John's Wort, an herbal medicine used for depression and mood disorders.

How to take FLUPHENAZINE:

- FLUPHENAZINE tablets must be taken orally by mouth.
- Take FLUPHENAZINE exactly as directed by your healthcare professional. Do not increase or decrease your dose, or stop taking FLUPHENAZINE without first consulting your healthcare professional.
- Your condition will not improve any faster but the risk of serious side effects will be increased.

Usual dose:

Your healthcare professional will tell you how many tablets to take, and when to take them each day. This may depend on your symptoms, age, health, and how you respond to FLUPHENAZINE. They may also increase or decrease your dose depending on your condition, especially during the first few days of your treatment. This is to find the lowest dose that works best to control your symptoms.

Overdose:

Symptoms of an overdose with FLUPHENAZINE may include:

- agitation,
- confusion,
- difficulty swallowing,
- dizziness,
- drowsiness,
- fainting,
- increased saliva production,
- muscle stiffness or twitching,
- loss of balance or coordination,
- low blood pressure, and

- weakness.

If you think you, or a person you are caring for, have taken too much FLUPHENAZINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss or forget a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regularly scheduled time. Do NOT double your dose to make up for the missed dose.

What are possible side effects from using FLUPHENAZINE?

These are not all the possible side effects you may have when taking FLUPHENAZINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- sweating,
- leaking of urine due to loss of bladder control (urinary incontinence),
- inability to empty all of the urine from the bladder (urinary retention),
- dizziness,
- drowsiness,
- dry mouth,
- nasal congestion,
- inability to tolerate light (photophobia),
- nausea,
- vomiting,
- headache,
- excitement,
- trouble falling and/or staying asleep,
- bizarre dreams,
- an increase in saliva,
- tongue changes,
- changes in appetite (increased or decreased),
- constipation,
- gastric irritation,
- change in sexual drive (altered libido),
- inability to ejaculate,
- skin rashes, itching and redness,
- menstrual cycle changes,
- enlargement of the breast tissue in men,
- weight changes,

- blurred vision,
- body temperature changes.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, asthma, wheezing, drop in blood pressure, feeling sick to your stomach, itchiness, or vomiting.			✓
Seizures (fits): loss of consciousness with uncontrollable shaking.			✓
Tardive dyskinesia (TD): uncontrollable, unusual, or abnormal movements, muscle twitches of the body, face, mouth, eyes or tongue, or stretching the neck and body.		✓	
UNKNOWN FREQUENCY			
Neuroleptic malignant syndrome (NMS): pronounced muscle stiffness inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion, or reduced consciousness.			✓
Extrapyramidal reactions: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want, masklike face (appears to lack emotion), tremors, drooling, or dragging feet as you walk, difficultly swallowing, a feeling of			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
restlessness, or inability to remain motionless.			
Heart problems: abnormally fast heartbeat, irregular heartbeat, chest pain, or changes in the rhythm of your heart.			✓
Priapism (persistent and painful erection of the penis lasting longer than 4 hours).			✓
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		✓	
Hypertension (high blood pressure): headaches, vision disorders, nausea, vomiting, shortness of breath, fatigue, dizziness, fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse, or heart palpitations.		✓	
Jaundice (build up of bilirubin in the blood)**:** yellowing of the skin and eyes, dark urine, light coloured stool, or itching all over your body.		✓	
Respiratory infection: fever, flu-like symptoms, coughing, or difficult or fast breathing.		✓	
Paralytic ileus (muscles that move food through the intestines are paralyzed): new or worsening constipation,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
nausea, vomiting, dehydration, gas, or abdominal pain.			
Eye problems: vision changes, blurred vision, sensitivity to light, pin point pupils, or other eye changes or disorder.			✓
Diabetic ketoacidosis (DKA; build): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, thirst, unusual fatigue, sleepiness, tiredness, a sweet or metallic taste in the mouth, sweet smelling breath, or different odour to urine or sweat.		✓	
Behavioural changes (including worsening of psychotic symptoms)**:** abnormal thoughts, hallucinations, delusions, changes in sleep patterns, confusion, anxiety, anger, speech that doesn't make sense, problems concentrating, disorientation, or agitation.			✓
Blood clots: swelling, pain, redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	
Blood disorders (low blood platelet, low white blood cell, and/or low red blood cell counts): frequent infection with fever, chills, sore throat, fatigue, aches, pains, flu-like symptoms, paleness of the skin, rapid heart rate, shortness of			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
breath, bruising easily, or heavy bleeding.			
Biliary stasis (bile flow from the liver is blocked): upper right abdominal pain, pain in the back, nausea, vomiting, or yellowing of the skin.			✓
Cerebral edema (swelling in the brain): severe headache, slow heartrate, irritability, weakness, difficulty talking, drowsiness, fainting, passing out, or vomiting.			✓
Hyperprolactinemia (increased levels of prolactin): In men: swelling in the breast, difficulty in getting or maintaining an erection, or other sexual dysfunction. In women: discomfort in the breasts, leaking of milk from the breasts (even if not pregnant), or missing your menstrual period or other problems with your cycle.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store FLUPHENAZINE at room temperature 15°C to 30°C. Keep container tightly closed. Protect from light.
- Keep out of the reach and sight of children.
- FLUPHENAZINE should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about FLUPHENAZINE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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