

## PRODUCT MONOGRAPH

Pr **MODECATE<sup>®</sup> CONCENTRATE**

Fluphenazine Decanoate Injection, B.P.

100 mg/ml

Antipsychotic

Bristol-Myers Squibb Canada  
Montréal, Canada

Date of Preparation:

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Date of Revision:

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**PRODUCT MONOGRAPH**  
**MODECATE CONCENTRATE**

Fluphenazine Decanoate Injection, B.P.

**THERAPEUTIC CLASSIFICATION**

ANTIPSYCHOTIC

**ACTION AND CLINICAL PHARMACOLOGY**

The effects of MODECATE CONCENTRATE (fluphenazine decanoate) are the same as those of fluphenazine hydrochloride, however, the slow release of the decanoate derivative of fluphenazine from the site of injection results in a prolonged duration of action. Once released in the blood, fluphenazine decanoate is rapidly hydrolyzed by blood esterases with no attenuation of its antipsychotic action. The onset of action generally appears between 24 to 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 and its use for maintenance therapy requires careful supervision.

Like other phenothiazines, fluphenazine exerts activity at various levels of the central nervous system as well as on peripheral organ systems which accounts for its antipsychotic action and side effects common to this class of drugs. Indirect evidence indicates that the antipsychotic effects of phenothiazines are linked to their effect in blocking dopamine and other catecholamine receptor sites.

Fluphenazine differs from some phenothiazine derivatives in several respects: it has less potentiating effect on central nervous system depressants and anesthetics than do some of the phenothiazines and appears to be less sedating. While hypotension may occur less frequently than with other phenothiazines, appropriate precautions should be observed when using fluphenazine decanoate (see PRECAUTIONS). Fluphenazine, however, is among the group of phenothiazines which exhibit a greater propensity for producing extrapyramidal reactions.

**PHARMACOKINETICS**

As with all antipsychotic drugs, fluphenazine is characterized by inter-individual variability in pharmacokinetics.

Fluphenazine is extensively metabolized, undergoing “first pass” metabolism by the liver, and is excreted in both the urine and the feces. Fluphenazine is highly protein-bound (greater than 90 %) in plasma.

Esterification of fluphenazine with a long-chain fatty acid and dissolving it in a sesame seed oil vehicle delays diffusion and availability of free drug released from the oily deposit site. Peak plasma concentration occurs within the first 24-hours after intramuscular injection of fluphenazine decanoate. The onset of action is generally between 24 and 72 hours after injection of fluphenazine decanoate, and the effects of drug on psychotic symptoms become significant within 48 to 96 hours. The serum half-life is approximately 7-10 days.

Phenothiazines cross the blood-brain barrier, cross the placenta easily, and cannot be removed by dialysis. It is not known whether fluphenazine is present in breast milk. However, other phenothiazines have been shown to be excreted in human breast milk.

## **INDICATIONS**

### **Adults**

MODECATE CONCENTRATE (fluphenazine decanoate) is a long-acting parenteral preparation, indicated in the management of manifestations of schizophrenia (see DOSAGE AND ADMINISTRATION).

Fluphenazine decanoate is not indicated for the management of severely agitated psychotic patients or psychoneurotic patients.

### **Geriatrics ( $\geq$ 65 years of age):**

Fluphenazine decanoate is not indicated for the management of geriatric patients with confusion and/or agitation.

### **Pediatrics (< 18 years of age):**

Fluphenazine decanoate is not intended for use in children under 18 years of age.

## **CONTRAINDICATIONS**

MODECATE (fluphenazine decanoate) is contraindicated in:

- Patients with a history of hypersensitivity to the active or inactive ingredients.
- Patients, who have shown hypersensitivity to other phenothiazines, including fluphenazine, should not be given fluphenazine decanoate as cross-sensitivity reactions may occur.
- Patients with marked cerebral atherosclerosis, suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures above 40° C may occur, sometimes not until 14-16 hours after drug administration.
- Patients with renal insufficiency, pheochromocytoma, or in patients with severe cardiovascular disorders.
- Patients who are comatose.

- Patients with severe CNS depression.
- Patients receiving large doses of CNS depressant medications (e.g., alcohol, barbiturates, narcotics, hypnotics, etc).
- Patients with blood dyscrasias.
- Patients with liver damage.

## **WARNINGS**

### **Elderly Patients with Dementia**

Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in elderly patients with dementia showed a mean 1.6 fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. 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. MODECATE is not indicated in dementia-related psychosis (see PRECAUTIONS, Use in the Elderly).

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

The use of this drug may impair the mental and physical abilities required for driving a car or operating heavy machinery particularly during the first days of therapy. Potentiation of the effects of alcohol may also occur.

### **Prolongation of the QT Interval**

As with other neuroleptics, very rare cases of QT interval prolongation have been reported with MODECATE. Neuroleptic phenothiazines may potentiate QT interval prolongation, which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation. (see also ADVERSE REACTIONS, Prolongation of QT Interval. As well, concomitant treatment with other drugs known to cause QT prolongation should be avoided (for more information, see Drug Interactions, Medicines that Prolong the QT Interval).

## **Use in Pregnancy**

### Teratogenic Effects

The safety of use in pregnant women has not been established. It is not known whether MODECATE CONCENTRATE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

### 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.

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

## **Use in Children**

The safety and efficacy of fluphenazine decanoate in children have not been established. Therefore, fluphenazine decanoate is not indicated for use in the pediatric age group (see INDICATIONS).

## **Tardive Dyskinesia**

Tardive dyskinesia (TD) is a syndrome of involuntary hyperkinetic abnormal movements that occur in predisposed individuals during or following the cessation of long-term neuroleptic drug therapy including fluphenazine. TD is characterized by involuntary, repetitive, purposeless hyperkinetic movements that involve the tongue, face, mouth, lips or jaw, trunk and extremities. The prevalence of TD greatly varies; when the mildest symptoms are included, prevalence can be 70%, whereas severe symptom rates are around 2.5%. The frequency and severity of TD increase with age, particularly in females.

The mechanism of TD is not known; though dopamine dysfunction is believed to underlie TD, it may be necessary but not sufficient to explain this complex disorder. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic 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 TD, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. However, neuroleptic treatment

itself suppresses the signs and symptoms of the syndrome thereby masking the underlying disease process.

Given these considerations, neuroleptic drugs should be prescribed in a manner that is most likely to minimize the occurrence of TD. Reducing the dose to the lowest effective level or discontinuing the drug for as long as possible continues to be the most rational approach. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

#### Neuroleptic Malignant Syndrome (Hyperthermia with Extrapyrimalidal and Autonomic Disturbances; Neuroleptic-Induced Hyperpyrexia)

Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs.

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

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 pathology.

The management of NMS should include 1) immediate discontinuation of all antipsychotic drugs including MODECATE® CONCENTRATE and other drugs not essential to 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 for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential re-introduction of therapy should be very carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

#### **Cerebrovascular Adverse Events (CVAEs), Including Stroke, in Elderly Patients with Dementia**

An increased risk of cerebrovascular adverse events has been seen in the dementia population in clinical trials with some atypical antipsychotics. The mechanism for this increased risk is not

known. There is insufficient data to know if there is an increased risk of cerebrovascular events associated with MODECATE. An increased risk however cannot be excluded. MODECATE is not indicated in elderly patients with dementia.

### **Vascular disease**

MODECATE should be used with caution in the patients with risk factors for stroke or with a history of stroke.

### **Venous thromboembolism**

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 preventive measures undertaken.

### **Benzyl alcohol and sesame oil (Excipients)**

This product contains 15 mg of benzyl alcohol per mL. Benzyl alcohol must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to three years old.

This product contains sesame oil, which may rarely cause severe allergic reactions.

### **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.

### **Genitourinary**

#### Priapism

Rare cases of priapism have been reported with antipsychotic use, such as MODECATE CONCENTRATE. 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**

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 MODECATE CONCENTRATE and then periodically throughout treatment (see ADVERSE REACTIONS).

### **Other Warnings**

The use of this drug may impair the mental and physical abilities required for driving or operating heavy machinery, particularly during the first days of therapy. Potentiation of the effects of alcohol may occur with the use of this drug (see Information to be Provided to Patient).

## **PRECAUTIONS**

### **Mortality in Elderly Patients with Dementia-related Psychosis**

In elderly patients with dementia-related psychosis, the efficacy and safety of MODECATE has not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. MODECATE is not indicated in patients with dementia-related psychosis.

### **Autonomic Nervous System Effects, including Blood Pressure Changes and Paralytic Ileus** (See also ADVERSE REACTIONS, Autonomic Nervous System)

Since hypotension and electrocardiographic changes suggestive of myocardial ischemia have been associated with the administration of phenothiazines, fluphenazine decanoate should be used with caution in patients with compensated cardiovascular or cerebrovascular disorders.

Hypotensive phenomena may develop in phenothiazine-treated patients who are undergoing surgery. Careful observation is necessary and anesthetic or central nervous system depressant dosages may have to be reduced.

The effects of anticholinergics may be potentiated in patients receiving fluphenazine because of added anticholinergic effects. Paralytic ileus, even resulting in death, may occur especially in the elderly. Fluphenazine decanoate should be used cautiously in patients exposed to extreme heat or phosphorus insecticides.

Fluphenazine should be used cautiously in patients exposed to extreme heat or phosphorous insecticides; in patients with a history of convulsive disorders (since grand mal convulsions have been known to occur in patients on therapy with fluphenazine); and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases, or pheochromocytoma.



**Blood Dyscrasias, Liver Damage** (see also ADVERSE REACTIONS, Hematologic and ADVERSE REACTIONS, Hepatic)

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

The possibility of liver damage, lenticular and corneal deposits, pigmentary retinopathy, and the development of irreversible dyskinesia should be borne in mind when patients are on prolonged therapy.

Alterations in Cephalin flocculation, alkaline phosphatase, sometimes accompanied by abnormalities in other liver function tests, have been reported in patients receiving esterified fluphenazine who have had no clinical evidence of liver damage. This, however, is not uncommon with phenothiazine therapy.

### **Convulsions**

Phenothiazines, particularly those with a long duration of action, should be used with caution in patients with a history of convulsive disorders since grand mal convulsions have been known to occur.

### **Allergic Cross-Sensitivity**

Because of the possibility of cross-sensitivity, MODECATE CONCENTRATE (fluphenazine decanoate) should be used with caution in patients who have developed cholestatic jaundice, and dermatoses or other allergic reactions to phenothiazine derivatives.

### **Silent Pneumonia**

As with other antipsychotic agents, the physician should be alert to the possible development of silent pneumonias in patients under treatment with phenothiazines.

### **Hyperprolactinemia**

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

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however,

have shown an association between chronic administration of these drugs and mammary tumorigenesis.

## **Drug Interactions**

Medicines that Prolong the QT Interval: Medicines that can prolong the QT interval should be avoided, as should any medicine that can cause electrolyte imbalance or an increase in the concentration of fluphenazine in the blood (see WARNINGS and ADVERSE REACTIONS). Medications that prolong the QT interval include dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, some other antipsychotics (e.g., mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide), sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. MODECATE should not be given with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in their respective Product Monograph as a contraindication or a warning.

P450 Enzyme substrates or inhibitors: Fluphenazine is metabolized by P450 2D6 and is itself an inhibitor of this drug-metabolizing 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 cardiac toxicity, anticholinergic side effects, or orthostatic hypotension.

CNS Depressants/Alcohol/Analgesics: The patient's response to alcohol and other CNS depressants such as hypnotics, sedatives or strong analgesics, may be exaggerated while taking MODECATE CONCENTRATE. Combined use with narcotic analgesics may cause hypotension as well as CNS or respiratory depression (see CONTRAINDICATIONS).

Tricyclic Antidepressants: Phenothiazines impair the metabolism of tricyclic antidepressants. Serum concentrations of both the tricyclic and phenothiazine are increased. Sedative and antimuscarinic effects may be potentiated or prolonged. Tricyclics may increase potential for arrhythmia.

Lithium: Neurotoxicity has been reported rarely when used concomitantly with fluphenazine.

ACE inhibitors / Thiazide Diuretics: Hypotension may result via additive or synergistic pharmacological activity.

Antihypertensives: The antihypertensive action of guanethidine, clonidine and possibly other adrenergic-blocking antihypertensive agents may be blocked. Clonidine may decrease the antipsychotic activity of phenothiazine.

Beta Blockers: Plasma levels of both drugs may be increased. Dosage reduction of both drugs is recommended.

Metrizamide: Phenothiazines may predispose patients to metrizamide-induced seizures. Discontinue for 48 hours prior to and for at least 24 hours after myelography.

Epinephrine and other sympathomimetics: Phenothiazines may antagonize the action of adrenaline and other sympathomimetics and may cause severe hypotension.

Antiparkinsonian medications: Phenothiazines may impair the anti-Parkinson effect of dopaminergic antiparkinsonian medications such as dopamine agonists and L-Dopa.

Anticholinergics / Antimuscarinics: Cholinergic blockade may be exaggerated when MODECATE CONCENTRATE is administered with anticholinergic agents, especially in older patients. Antimuscarinic effects may be potentiated or prolonged. Close supervision and careful dosage adjustment are required when MODECATE CONCENTRATE is used with other anticholinergic or antimuscarinic drugs.

Anticonvulsants: Anticonvulsant action may be impaired by MODECATE CONCENTRATE.

Anticoagulants: Phenothiazines may alter the effects of anticoagulants.

Antidiabetics: Phenothiazines have been associated rarely with loss of blood glucose control in patients with diabetes.

Cimetidine: Cimetidine may reduce plasma concentrations of phenothiazines.

Antacids / Antidiarrheal Agents: Concurrent administration may interfere with absorption. Administration of antacids should be spaced at least 1 hour before or 2-3 hours after fluphenazine dose.

Amphetamine / Anorectic Agents: Concurrent administration may produce antagonistic pharmacologic effects.

### **Abrupt Withdrawal**

In general, phenothiazines do not produce psychic dependence; however, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high-dose therapy. Reports suggest that these symptoms can be reduced if concomitant antiparkinson agents are continued for several weeks after the phenothiazine is withdrawn.

### **Use in the Elderly**

Antipsychotic drugs should be used with care in elderly patients (>60 years old), as these patients have a greater potential for adverse effects.

Doses in the lower range (1/4 to 1/3 of those in younger adults) should be sufficient for most elderly patients. Response should be monitored and dose adjusted. If an increase is necessary, doses should be gradually increased (See DOSAGE and ADMINISTRATION).

## **Information to Be Provided to Patients**

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Patients should also be warned that fluphenazine may 1) impair their ability to perform activities requiring mental alertness or physical coordination, 2) enhance their response to alcohol, barbiturates or other CNS depressants, and 3) increase their vulnerability when exposed to temperature extremes, possibly resulting in hyperthermia or hypothermia.

## **ADVERSE REACTIONS**

### **Central Nervous System**

#### **(i) Extrapyramidal Symptoms**

The adverse events most frequently reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism (tremor, rigidity, etc.), dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Most often these extrapyramidal symptoms are reversible; however, they may be persistent. With any given phenothiazine derivative, the incidence and severity of such events depend more on individual patient sensitivity than on other factors, but dosage level and patient age are also determinants.

MODECATE CONCENTRATE (fluphenazine decanoate) produces a higher incidence of extrapyramidal reactions than the less potent piperazine derivatives or the straight-chain phenothiazines such as chlorpromazine. Extrapyramidal reactions tend to occur in the first few days after an injection of fluphenazine decanoate. Caution should be exercised in those who have marked extrapyramidal reactions to oral phenothiazines or similar drugs, particularly elderly females. Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These symptoms can usually be controlled by administration of anticholinergic or antiparkinson drugs (such as benztropine mesylate) and by subsequent reduction in dosage.

The use of prophylactic antiparkinson medication may be considered, although its therapeutic value has not yet been established.

#### **(ii) Tardive Dyskinesia (See WARNINGS, Tardive Dyskinesia)**

The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing

movements). Sometimes, these may be accompanied by involuntary movements of the trunk and the extremities. The severity of the syndrome and the degree of impairment produced vary widely.

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may occur upon dosage reduction or after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents do not alleviate the symptoms of this syndrome.

Neuroleptic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Reducing the dose to the lowest effective level or discontinuing the drug for as long as possible continues to be the most rational approach. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

### (iii) Other CNS Effects

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 high dosages of fluphenazine. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered. In some patients, phenothiazine derivatives have been known to cause restlessness, excitement, or bizarre dreams.

Rare occurrences of **neuroleptic malignant syndrome (NMS)** have been reported in patients on neuroleptic therapy. The syndrome is characterized by hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leukocytosis, fever, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal (see WARNINGS, Neuroleptic Malignant Syndrome).

### **Prolongation of the QT interval:**

QT prolongation, ventricular arrhythmias, ventricular fibrillation, ventricular tachycardia, cardiac arrest, torsades de pointes and sudden unexplained death are class effects of phenothiazines. (See WARNINGS, Prolongation of the QT Interval, and PRECAUTIONS, Drug Interactions).

### **Cerebrovascular Stroke-like Events:**

An approximately 3-fold increased risk, compared to placebo, of cerebrovascular adverse events, such as stroke and transient ischemic attacks as well as death, has been seen in randomized, placebo-controlled clinical trials, in the dementia population with some atypical antipsychotics. Fluphenazine should be used with caution in the elderly with dementia. (See WARNINGS, Cerebrovascular Events, Including Stroke, in Elderly Patients with Dementia).

### **Autonomic Nervous System** (see also WARNINGS)

Hypotension, hypertension and fluctuations in blood pressure have been reported with fluphenazine.

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.

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.

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

### **Metabolic and Endocrine**

Weight change, peripheral edema, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and libido changes in women have all been known to occur in some patients on phenothiazine therapy.

### **Allergic Reactions**

Skin disorders such as itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

## **Hematologic**

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use in the post-marketing setting. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting MODECATE CONCENTRATE and then periodically throughout treatment (see WARNINGS).

Leukopenia, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have also been observed with phenothiazine derivatives. 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 (see WARNINGS).

## **Hepatic**

Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests and hepatitis, has been reported in patients receiving the enanthate ester of fluphenazine (a closely related compound).

## **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 flare-ups of psychotic behaviour patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions.

Potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur (see CONTRAINDICATIONS).

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

Venous thromboembolism, including fatal pulmonary embolism and deep vein thrombosis, has been reported with antipsychotic drugs, including fluphenazine, in case reports and/or observational studies.

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

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

For management of a suspected drug overdose, please contact your regional Poison Control Center.

Symptoms of overdose will likely be manifested as severe extrapyramidal reactions, hypotension or sedation. CNS depression may progress to coma with areflexia. Restlessness, confusion and excitement may occur with early or mild intoxication. The drug should be withdrawn and the symptoms of overdose treated supportively. Initial hospitalization may be required in cases of large overdose and close medical supervision should be maintained throughout the duration of drug action. Up to several hours after an oral overdose, gastric lavage should be attempted, followed by activated charcoal and then cathartics.

An airway should be maintained. If severe hypotension should occur, supportive measures including the use of intravenous vasopressor drugs should be instituted immediately. Levarterenol bitartrate Injection, U.S.P. 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.

Extrapyramidal symptoms may be treated with antiparkinsonian agents, and should be continued for several weeks. Antiparkinson medication should be withdrawn gradually to avoid the emergence of rebound extrapyramidal symptoms.

Limited experience indicates that phenothiazines are not dialyzable. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis are ineffective in phenothiazine poisoning.

For up-to-date information on the management of a suspected drug overdose, contact the regional Poison Control Centre.

## **DOSAGE AND ADMINISTRATION**

MODECATE CONCENTRATE (fluphenazine decanoate injection) is usually given as an intramuscular injection preferably in the gluteus maximus, although it may also be administered subcutaneously. MODECATE CONCENTRATE is not for intravenous use.

A dry syringe with a needle of at least 21 gauge should be used to inject MODECATE CONCENTRATE. Use of a wet needle or syringe may cause the solution to become cloudy.

As a long-acting depot fluphenazine, fluphenazine decanoate has been found useful in the maintenance treatment of non-agitated, chronic schizophrenic patients who have been



stabilized with short-acting neuroleptics and might benefit from transfer to a longer-acting injectable medication. The changeover of medication should aim at maintaining a clinical outcome similar to, or better than, that obtained with the previous therapy. To achieve and maintain the optimum dose, the changeover from other neuroleptic medication should proceed gradually and constant supervision is required during the period of dosage adjustment in order to minimize the risk of overdosage or insufficient suppression of psychotic symptoms before the next injection.

### Adult Patients

The initial recommended dose is 2.5 mg to 12.5 mg. An initial dose of 12.5 mg is usually well tolerated.

The onset of action generally appears between 24 to 72 hours after injection, and the effects of the drug on psychotic symptoms become significant within 48 to 96 hours.

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

Subsequent doses and frequency of administration must be determined for each patient. There is no reliable dosage comparability between a short-acting neuroleptic and depot fluphenazine and, therefore, the dosage of the long-acting drug must be individualized. Except in particularly sensitive patients, a second dose of 12.5 mg or 25 mg can be given 4 to 10 days after the initial injection. Subsequent dosage adjustments are made in accordance with the clinical circumstances and the response of the patient. Patients can usually be controlled with 25 mg or less, every two to three weeks. Although doses greater than 50 mg are usually not deemed necessary, doses up to 100 mg have been used in some patients. If doses greater than 50 mg are necessary, the next dose and succeeding doses should be increased in increments of 12.5 mg. While the response to a single injection lasts usually two to three weeks, it may last for four weeks or more.

After an appropriate dosage adjustment is achieved, regular and continuous supervision and reassessment is considered essential in order to permit any further dosage adjustments that might be required to ensure use of the lowest effective individual dose and avoid troublesome side-effects.

Since higher doses increase the incidence of extrapyramidal reactions and other adverse effects, the amount of drug used should not be increased in order to prolong the intervals between injections. With higher doses, there is also more variability in the action of depot fluphenazine.

MODECATE CONCENTRATE (100 mg/mL) may be administered in patients who complain of discomfort with a large injection volume or when a smaller injection volume is desirable.

### Elderly Patients

The suggested initial test dose is 2.5 mg, gradually adjusted according to the response of the patient. Maintenance doses in the lower range (1/4 to 1/3 of those in younger adults) may be sufficient for most elderly patients.

### “Poor Risk” Patients

Modecate is contraindicated in patients with known hypersensitivity to phenothiazines (see CONTRAINDICATIONS). For patients with disorders that predispose to undue reactions (see WARNINGS, PRECAUTIONS), therapy may be initiated cautiously with oral or parenteral fluphenazine hydrochloride. When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of MODECATE may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient.

## PHARMACEUTICAL INFORMATION

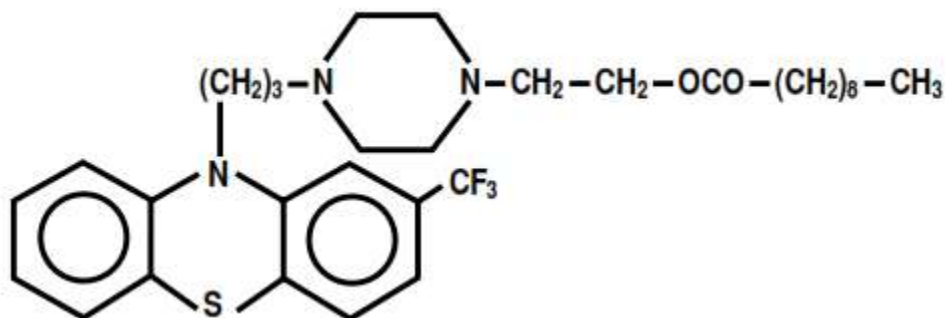
### **Drug Substance**

Proper Name: Fluphenazine decanoate

Chemical Name:

2-[4-[3-[2-(Trifluoromethyl)-10H-phenothiazine-10yl]propyl] piperazin-1-yl]ethyl decanoate

Structural Formula:



Molecular Formula:  $\text{C}_{32}\text{H}_{44}\text{F}_3\text{N}_3\text{O}_2\text{S}$

Molecular Weight: 591.79

Description: Fluphenazine decanoate is insoluble in water and is light-sensitive.

## AVAILABILITY

MODECATE CONCENTRATE is available in 1 mL ampoules containing 100 mg/mL fluphenazine decanoate in solution in sesame oil. Benzyl alcohol, 1.5%, is added as a preservative.

Storage: Do not store above 25 °C. Do not refrigerate or freeze. Protect from light..

## **PHARMACOLOGY**

Single doses of fluphenazine decanoate exerted long-lasting pharmacological effects in several species.

Fluphenazine decanoate protected mice from amphetamine-induced group toxicity. Five, 10 and 20 mg/kg doses protected 20, 30 and 50% of the mice, respectively, from the lethal effect of amphetamine. The protective effect of a single dose lasted for 21 days.

Fluphenazine decanoate 35 mg/kg, inhibited the conditioned avoidance response in rats by 50 to 60%. Inhibition was maximal two to ten days after injection. Conditioned avoidance behavior was still inhibited by 25%, 50 to 55 days after injection, indicating that this behavior returns to baseline only very slowly. Two subsequent injections, at monthly intervals, kept the conditioned avoidance response suppressed by 50 to 70%.

Fluphenazine decanoate, 5 and 10 mg/kg, antagonized the apomorphine-induced stereotyped behavior in rats for 10 and 21 days, respectively.

Fluphenazine decanoate, 8.6 mg/kg, protected dogs from the emetic effect of apomorphine for up to 28 days.

Fluphenazine decanoate also induced sedation and ataxia in dogs and a decrease in rectal temperature. The drug also produced moderate hypotension in unanesthetized dogs, dose-related hypotension in anesthetized dogs and marked hypotension in anesthetized, curarized cats.

Pharmacokinetic studies of fluphenazine decanoate in dogs have demonstrated that the excretion rate is dependent upon the rate of release from the injection site. Fluphenazine decanoate is hydrolysed by plasma esterases to fluphenazine and appears in the bile as the glucuronide of 7-hydroxy-fluphenazine. Only 1-3% of an intramuscular dose is excreted in the urine, the remainder appearing in the feces. Uptake of fluphenazine-C14 into the brain does not show any striking localization.

## **TOXICOLOGY**

### **Acute Toxicity**

| <b>Species</b> | <b>Route</b> | <b>LD50 (mg/kg)</b> |
|----------------|--------------|---------------------|
| Mice           | s.c.         | 510                 |
| Rat            | i.p.         | 750960820           |
| Rat            | s.c.         | 968                 |

### Subacute and Chronic Toxicity

| Species | Route | Doses (mg/kg/wk) | Duration | Comments   |
|---------|-------|------------------|----------|--|
| Rat     | s.c.  | 30, 10, 3        | 3 months | Depression proportion to dosage. Growth retardation, reversible upon discontinuation. No morphological evidence of toxicity.   |
| Rat     | s.c.  | 50, 25, 10       | 3 months | Catalepsy after injection. 1/10 males at 10 mg/kg/wk; recovered day 3. 1/10 males at 25 mg/kg/wk; recovered day 3. 5/10 males at 50 mg/kg/wk; recovered day 5.   |
| Dog     | s.c.  | 90, 30, 10       | 3 months | Reduced activity, miosis, prolapsed nictating membrane and tremors - decreased with time. No morphological evidence of toxicity.   |
| Dog     | s.c.  | 10               | 3 months | No catalepsy. No histological anomalies.   |
| Rat     | s.c.  | 30, 10, 3        | 6 months | Decreased activity and apathy (not dose-related). Decreased body weight gain and food utilization. Slight hypertrophy of mammary glands and lactation. Increased pituitary weight in males. Decreased adrenal weight in females. |

### Reproduction

| Species | Sex | Dose (mg/kg) | Route | Times of Administration | Comments  |
|---------|-----|--------------|-------|-------------------------|---|
| Rabbit  | F   | 0.84, 5.6    | s.c.  | Day 6 of gestation      | No teratogenic effects. Possible interference with nidation. Delayed ossification in high dose group (may be related to other factors.) |

| Species | Sex | Dose (mg/kg) | Route | Times of Administration  | Comments   |
|---------|-----|--------------|-------|--|--|
| Rat     | F   | 0.5, 2.5     | s.c.  | Once weekly; 2 weeks before mating and throughout gestation and lactation. | Index of fertility decreased in 2.5 mg/kg/wk group. Follow-up study showed normal spermatogenesis and abundant sperms in epididymis. |
|         | M   | 0.5, 2.5     | s.c.  | Once weekly; 10 weeks before mating.                                       |  |
| Rat     | F   | 0.5, 2.5     | s.c.  | Day 8 of gestation   | No teratogenic changes or effects upon fetal development.  |
| Rat     | F   | 0.5, 2.5     | s.c.  | Day 15 of gestation  | No significant adverse effects observed.   |

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## CONSUMER INFORMATION

### MODECATE® CONCENTRATE

#### Fluphenazine Decanoate Injection, B.P.

This leaflet is part III of a three-part "Product Monograph" published when MODECATE® CONCENTRATE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MODECATE® CONCENTRATE. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

MODECATE® CONCENTRATE belongs to a group of medicines called antipsychotic drugs (medications used to treat mental illnesses associated with psychosis).

MODECATE® CONCENTRATE is used to treat the symptoms of schizophrenia, which may include hallucinations (hearing and seeing things that are not there), delusions (false beliefs based on an incorrect interpretation of reality), unusual suspiciousness, emotional withdrawal. Patients suffering from schizophrenia may also feel depressed, anxious or tense.

Ask your doctor if you have any questions about why MODECATE® CONCENTRATE has been prescribed to you.

#### What it does:

Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how MODECATE®

CONCENTRATE works is unknown. However, it seems to readjust the balance of dopamine and serotonin. MODECATE® CONCENTRATE usually begins to work within 1 to 3 days after injection, with a full effect on symptoms usually occurring within 2 to 4 days.

#### When it should not be used:

Do not use MODECATE® CONCENTRATE if you:

- are allergic to fluphenazine decanoate, to phenothiazines (a type of antipsychotic) or to any of the ingredients in the product (see the section "What the non-medicinal ingredients are"). Signs of allergic reaction may include a rash, itching, shortness of breath or swelling of the face, lips or tongue.
- have a tumour on the adrenal gland called a 'pheochromocytoma'
- have severe heart problems
- have severe liver or kidney problems
- take large quantities of alcohol or take medicines such as barbiturates, narcotics or hypnotics
- have a blood disorder
- have brain damage

MODECATE® CONCENTRATE is not for use in children under the age of 18.

#### What the medicinal ingredient is:

fluphenazine decanoate

#### What the nonmedicinal ingredients are:

The solution contains sesame oil. Benzyl alcohol, 1.5%, is added as a preservative.



**What dosage forms it comes in:**

MODECATE® CONCENTRATE is for injection only into the muscle or under the skin. One ampoule of MODECATE® CONCENTRATE contains 100 mg/mL fluphenazine decanoate.

- have or have ever had breast cancer
- have or have ever had adrenal tumors
- drink alcoholic beverages or use recreational drugs
- have ever abused drugs
- are exposed to extreme heat
- plan to have surgery or a procedure requiring anesthetics

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

Studies with various medicines of the group to which MODECATE® CONCENTRATE belongs, when used in the elderly patients with dementia, have been associated with an increased rate of death. MODECATE® CONCENTRATE is not indicated in elderly patients with dementia.

Before using MODECATE® CONCENTRATE, tell your doctor or pharmacist if you:

- are taking any other medicines (prescriptions or over the counter medicines or natural products)
- suffer from or have a history of heart or blood vessel diseases
- have a history of strokes or mini-strokes (transient ischemic attacks)
- have abnormal blood pressure, slow heart beat
- are an elderly patient suffering from dementia (loss of memory and other mental abilities due to Alzheimer disease or other conditions)
- have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral contraceptives (“The Pill”).
- have or develop involuntary, irregular muscle movements, especially in the face
- are pregnant, think you are pregnant, or plan to become pregnant. You should not take MODECATE® CONCENTRATE unless you have discussed this with your doctor
- are breast-feeding or plan to breastfeed
- have ever had blackouts or seizures

**Effects on Newborns:**

In some cases, babies born to a mother taking fluphenazine during pregnancy have experienced symptoms that are severe and require the newborns to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

During the first few days of treatment, MODECATE® CONCENTRATE may cause some people to become drowsy or less alert. You should not drive a car, operate machinery or participate in activities requiring alertness until you are sure MODECATE® CONCENTRATE does not affect you.

MODECATE® CONCENTRATE may also interfere with the ability of the body to adjust to temperature extremes, possibly resulting in hyperthermia or hypothermia. (increase or decrease below normal levels of body temperature) symptoms include: muscle stiffness, confusion, fast or irregular pulse or blood pressure, and sweating.

Avoid being exposed to heat, and tell your doctor if you may be exposed to heat.

Occasional blood tests to check your liver function should be done while you are taking MODECATE® CONCENTRATE. Kidney function tests should also be done if you are taking it long term.

During or following long-term treatment with MODECATE® CONCENTRATE muscle twitching or uncontrolled movements of the mouth, tongue, face

or jaw may occur in some patients. For some patients, this side effect may **not** go away after MODECATE® CONCENTRATE treatment is stopped. Tell your doctor immediately if you experience these symptoms.

## INTERACTIONS WITH THIS MEDICATION

Tell all doctors, dentists or pharmacists who are treating you that you are taking MODECATE® CONCENTRATE. Tell them if you are taking, have recently taken or are planning on taking any other medicines, including medicines obtained without a prescription and natural products. Your doctor or pharmacist will tell you which medicines you can take with MODECATE® CONCENTRATE.

MODECATE® CONCENTRATE can add to the effects of alcohol and drugs that reduce the ability to react (e.g., tranquilizers, narcotic painkillers, certain drugs for allergies, sleep, seizures, depression, and mental illness). You should avoid consuming alcoholic beverages and only take drugs prescribed by your doctor while on MODECATE® CONCENTRATE therapy.

Inform your doctor if you start or stop taking any of the following medications:

- medications used to treat Parkinson's disease, such as dopamine agonists levodopa as these may decrease the effect of MODECATE® CONCENTRATE
- heart medications (e.g., medications for high blood pressure, antiarrhythmics – medications for rhythm disorders), as these may interact with MODECATE® CONCENTRATE to cause your blood pressure to drop too low
- medications that may change the electrical activity of the heart, such as but not restricted to: medicines for malaria, heart rhythm

disorders, allergies, other antipsychotics, antidepressants, water tablets or other medicines affecting body salts (sodium, potassium, magnesium

- drugs for epilepsy and diabetes, blood thinners, antacids (e.g., Pepto-Bismol, Maalox) and antidiarrheal agents (e.g., loperamide)
- Lithium, a medicine used to calm emotions and treat mental illness
- Anticholinergic medicines such as some medicines used for irritable bowel syndrome, asthma or incontinence
- Some medicines used for life threatening allergic reactions or conditions, such as adrenaline
- Metrizamide – used to help with tests such as X-ray examinations
- Amphetamines – used for Attention Deficit Hyperactive Disorder (ADHD)
- Sedatives or alcohol.

If you need surgery, be sure to tell your doctor that you are taking MODECATE® CONCENTRATE as you may be at risk of developing low blood pressure.

Patients should avoid being exposed to phosphorous insecticides.

## PROPER USE OF THIS MEDICATION

### Usual dose:

MODECATE® CONCENTRATE will usually be given as an injection in a muscle; however, it may also be given under the skin. Your doctor will decide the best dose for you based on your individual needs.

The recommended starting dose is 2.5 mg to 12.5 mg.

A second dose may be given to you 4 to 10 days later. Elderly patients may need lower doses.

Depending how you respond, your doctor will decide the best dose and interval between injections for you.

MODECATE® CONCENTRATE is not for intravenous use.

### **Overdose:**

In case of drug overdose, contact a healthcare practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Having too much MODECATE® CONCENTRATE may make you feel drowsy and you may become unconscious. You may also feel very cold, have a fast or irregular heartbeat, severe muscle spasms or involuntary movements.

### **Missed Dose:**

If you miss an appointment, you should contact your doctor right away to let him or her know you missed your injection. Your doctor will then advise you when to come for your next scheduled appointment.

## **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

MODECATE® CONCENTRATE, like any medication, may cause side effects. These side effects are most likely to be minor and temporary; however, some may be serious and need medical attention. Many of the side effects are dose related, so it is important to find the right dose with your doctor. Should you experience side effects, discuss them with

your doctor.

The most common side effects of MODECATE® CONCENTRATE include:

- sleeplessness/sleepiness
- anxiety
- trembling, decreased motor function or activity such as slight muscle stiffness
- muscle twitching or abnormal uncontrolled movements of the mouth, tongue, face or jaw
- restlessness
- dizziness
- headache
- constipation
- dryness of the mouth
- fever, nausea and loss of appetite, vomiting
- weight change
- menstrual and libido changes,
- abnormal lactation in women
- impotence and breast enlargement in men
- blurred vision,
- increased urination

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Your doctor should check your body weight before starting MODECATE® CONCENTRATE and continue to monitor your weight for as long as you are being treated.

Your doctor should take blood tests before starting MODECATE® CONCENTRATE to monitor your

blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to

monitor your blood for as long as you are treated.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect |   | Talk with your doctor or pharmacist |              | Stop taking the drug and seek immediate emergency medical treatment |
|------------------|---|-------------------------------------|--------------|---|
|                  |   | Only if severe                      | In all cases |   |
| Uncommon         | Low blood pressure and feeling of dizziness, especially when getting up from a lying or sitting position  |                                     | √            |   |
|                  | Skin rash, itching, shortness of breath or swelling of the face, lips or tongue   |                                     |              | √   |
|                  | Soreness of the mouth, gums or throat or any symptoms of upper respiratory infection, unexplained fever or itching  |                                     | √            |   |
|                  | Yellowing of the skin or eyes, dark urine   |                                     | √            |   |
|                  | Fast or irregular heartbeat   |                                     | √            |   |
|                  | Sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech or vision problems, even for a short period of time. |                                     |              | √   |
|                  | Dizziness, palpitations, or episodes of fainting  |                                     | √            |   |
|                  | Tremor, muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling  |                                     | √            |   |
|                  | Severe muscle stiffness, increased sweating, fever, fast or irregular heartbeat, high or low blood pressure, difficult or fast breathing, decreased urine production and confusion  |                                     |              | √   |
|                  | Muscle twitching or uncontrolled movements of the mouth, tongue, face or jaw can occur after long-term therapy or after you stop using the drug                                     |                                     | √            |   |
| Rare             | Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.                 |                                     | √            |   |
| --               | Long-lasting (greater than 4 hours in duration) and painful erection of the penis.  |                                     |              | √   |
|                  | New or worsening constipation this may be a sign of paralytic ileus (paralysis of the intestines)   |                                     | √            |   |
|                  | Glaucoma (increased pressure within the eyeballs)   |                                     | √            |   |
|                  | Convulsions, epileptic fits   |                                     |              | √   |
|                  | Pneumonia (infection of the lungs possibly without symptoms)  |                                     | √            |   |
|                  | Swelling of the hands or feet   |                                     | √            |   |

*This is not a complete list of side effects. For any unexpected effects while taking MODECATE® CONCENTRATE, contact your doctor or pharmacist.*

## HOW TO STORE IT

MODECATE® CONCENTRATE should not be stored above 25°C. Do not refrigerate or freeze. Protect from light.

Keep MODECATE® CONCENTRATE out of the reach of children.

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at:  
<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 1908C  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reactions reporting guidelines are available on the MedEffect™ Canada Web site at  
<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>

*Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be found at

www.bmscanada.ca or obtained by contacting the sponsor, Bristol-Myers Squibb Canada, at 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada.

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