PRODUCT INFORMATION

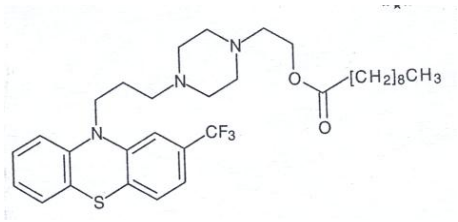
MODECATE
(Fluphenazine Decanoate Oily Injection)

NAME OF DRUG

Fluphenazine decanoate.

DESCRIPTION

Chemically fluphenazine decanoate is 2-[4-[3-[2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]propyl] piperazin -1-yl] ethyl decanoate. The empiric formula is $C_{32}H_{44}F_3N_3O_2S$ and the molecular weight 591.8.
The chemical structure is



The CAS registry number is 5002-47-1.

It is a pale yellow viscous liquid or a yellow solid that is practically insoluble in water.

Modecate injection is fluphenazine decanoate in sesame oil with 1.5% benzyl alcohol.

PHARMACOLOGY

Fluphenazine is an antipsychotic agent of the phenothiazine class possessing a piperazine side chain. The basic effects of Modecate appear to be no different from those of fluphenazine hydrochloride, with the exception of duration of action. The esterification of fluphenazine markedly prolongs the drug's duration of effect without unduly attenuating its beneficial action. Fluphenazine has activity at all levels of the CNS as well as on multiple organ systems. The mechanism of therapeutic action is unknown, but may be related to anti-dopaminergic effects of the drug. Fluphenazine has affinity for D1 and D2 receptors, resulting in antagonistic effects at these receptors. Fluphenazine raises serum prolactin levels due to anti-dopaminergic actions. Anticholinergic (antimuscarinic) effects occur and are responsible for some of fluphenazine's adverse effects.

Pharmacokinetics
Fluphenazine is extensively metabolized, undergoing "first pass" metabolism by the liver, and is excreted in both the urine and faeces. 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 depot site following intramuscular injection. Peak plasma concentration occurs within the first 24 hours after injection of 25mg of Modecate intramuscularly as a single injection. The onset of action is generally between 24 and 72 hours after injection of Modecate, and the effects of drug on psychotic symptoms become significant within 48 to 96 hours. The serum half-life is approximately 7-10 days, but this could be longer on chronic dosing.

A therapeutic plasma level "window" for fluphenazine between 0.5 and 2.5 ng/mL has been proposed. 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

Modecate is indicated in the management of manifestations of schizophrenia.

Modecate has not been shown to be effective in the management of behavioural complications in patients with mental retardation.

Note: Modecate is not intended for use in non-psychotic disorders.

CONTRAINDICATIONS

Phenothiazines are contraindicated in patients with suspected or established subcortical brain damage

Modecate should not be used in patients receiving large doses of CNS depressants (alcohol, barbiturates, narcotics, hypnotics etc).

Modecate is contraindicated in comatose or severely depressed states.

The presence of blood dyscrasia, bone marrow depression, marked cerebral atherosclerosis, liver damage, or renal insufficiency precludes the use of Modecate.

It is not intended for use in children under 12 years.

Modecate is also contraindicated in patients with a history of hypersensitivity to the active and inactive ingredients; cross sensitivity to phenothiazine derivatives may occur.

PRECAUTIONS

Physicians should be alert to the possibility that severe adverse reactions may occur which require immediate medical attention. Outside hospitals or other psychiatric institutions, Modecate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs, particularly phenothiazine derivatives. Facilities should be available for periodic checking of hepatic function, renal function, and the blood picture. During the first 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 serum urea becomes abnormal, treatment should be discontinued. Patients receiving prolonged Modecate therapy with moderate to high dosages should have periodic ophthalmologic examinations as pigmentary retinopathy, lenticular and corneal deposits may occur (see **ADVERSE REACTIONS**).

Tardive Dyskinesia

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs, including phenothiazine (see **ADVERSE REACTIONS**). Although the prevalence of the syndrome appears to be greater in elderly patients, patients with organic brain damage and females, it is impossible to rely upon prevalence estimates to predict which patients are likely to develop the syndrome. Other risk factors include affective disorder and schizophrenia characterised by negative symptoms.

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 antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after 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 treatment is withdrawn. Antipsychotic treatment itself including fluphenazine, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, Modecate should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia. Chronic Modecate treatment should generally be reserved for patients who suffer from chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do 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 while on Modecate, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (See **ADVERSE REACTIONS –Tardive Dyskinesia)**

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

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 and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias), dyspnoea and akinesia, sometimes progressing to stupor or coma. Additional signs may include leucocytosis, elevated creatine kinase, liver function abnormalities, acute renal failure and rhabdomyolysis.

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 (eg: 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. See Adverse Reactions.

Cross Sensitivity
Because of the possibility of cross sensitivity, Modecate is contraindicated for use in patients with known phenothiazine hypersensitivity (see **CONTRAINDICATIONS**), including those who have developed cholestatic jaundice, bone marrow suppression, blood dyscrasias, dermatoses, or other allergic reactions to phenothiazine derivatives.

Surgery
Psychotic patients on large doses of Modecate who are undergoing surgery should be watched carefully for possible hypotensive phenomenon. Moreover, it should be remembered that reduced amounts of anaesthetics or CNS depressants may be necessary.

Anticholinergic Effects
Modecate should be used with caution in patients with prostatic hypertrophy, closed-angle glaucoma, paralytic ileus or urinary retention as the anticholinergic activity of Modecate may exacerbate these conditions. Modecate may also increase the anticholinergic effects of organophosphorus insecticides.

Temperature
Because phenothiazines depress the hypothalamic mechanism for regulation of body temperature, Modecate should be administered with caution to patients exposed to extreme heat or cold. Patients should be advised that they are likely to have increased vulnerability when exposed to temperature extremes, possibly resulting in hyperthermia or hypothermia.

Photosensitivity
Photosensitivity may occur with the use of phenothiazines. Patients on Modecate should avoid undue sunlight (UV) exposure and the use of tanning beds. Patients should be advised to use sunscreens when exposed to sunlight for significant lengths of time.

Seizure Disorders
Phenothiazines may lower the seizure threshold. Modecate should be used with caution in patients with a history of seizure disorders, epilepsy, EEG abnormalities or in those receiving anticonvulsant/antiepileptic drugs as grand mal convulsions have been known to occur. If fluphenazine therapy is needed, Modecate should be initiated with a low dosage and titrated upward slowly to desired clinical effect. Abrupt increases in Modecate dosage should be avoided.

Prolongation of the QT interval
Since phenothiazines can prolong the QT interval, caution should be used when treating patients with cardiovascular disease, or congenital or acquired QT interval prolongation.
Concomitant treatment with other drugs known to cause QT prolongation should be avoided. (See **PRECAUTIONS - Interactions – Drug that prolong QT Interval and ADVERSE REACTIONS**)

Cerebrovascular Events
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized, placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Fluphenazine should be used with caution in patients with risk factors for stroke. Potentiation of the effects of alcohol may occur with the use of this drug.

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

Increased Mortality in Elderly People with Dementia:
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Other Medical Conditions
Since hypotension and ECG changes suggestive of myocardial ischaemia have been associated with the administration of phenothiazines, Modecate should be used with caution in patients with mitral, cerebrovascular, cardiovascular, respiratory or renal insufficiency, and in patients with phaeochromocytoma. Other conditions (such as existing tachycardia or cardiac insufficiency) in which it may be undesirable to lower the patient's blood pressure) require caution also. Blood pressure measurements should be taken periodically to detect hypotension.

Should hypotension occur and a vasopressor be required, adrenaline should not be used since fluphenazine may block its vasopressor activity and further lowering of blood pressure may occur. Instead, noradrenaline or metaraminol should be used.

Modecate should be used with caution or not at all in patients with Parkinson's disease as central blockage of dopamine (D_2) receptors by phenothiazines may dramatically worsen the extrapyramidal symptoms of Parkinson's disease.

Modecate should also be used with caution or not at all in patients with diabetes mellitus, hypothyroidism, myasthenia gravis or prostatic hyperplasia. Fluphenazine may impair blood sugar control in diabetic patients.

Modecate should be administered with caution and in reduced dosage to patients who have exhibited severe reactions to insulin or electroconvulsive therapy (ECT).

Modecate should be used with caution in patients with hypocalcaemia since these patients appear to be more susceptible to dystonic reactions.

Because neurologic reactions resulting from phenothiazine therapy may be similar to CNS signs and symptoms accompanying certain disorders (such as encephalitis, Reye's syndrome, encephalopathy, meningitis and tetanus), the diagnosis of these disorders may be incorrectly diagnosed as drug induced.

The antiemetic effect of fluphenazine may mask the signs and symptoms of overdosage of toxic drugs (eg. vomiting due to antineoplastic agents, ototoxicity of aminoglycosides) or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumour.

Prolonged Treatment
The possibility of liver or kidney damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia should be remembered when patients are

on prolonged therapy. Renal function of patients on long-term therapy should be monitored; if BUN becomes abnormal, treatment should be discontinued.

Haematologic Disorders
Modecate should be used with caution in patients with pre-existing haematological disease (see **CONTRAINDICATIONS**). Though rare, agranulocytosis and other haematologic disorders have been reported with the use of phenothiazines. Patients should report the appearance of fever, sore throat, lethargy or other signs of decreased blood cell counts or infection to their doctor immediately. Serum blood counts with differentials should be monitored periodically. Modecate may need to be discontinued if significant suppression of blood counts occurs.

Silent Pneumonias
As with any phenothiazine, the physician should be alert to the possible development of silent pneumonias in patients under treatment with Modecate.

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.

Effect on Ability to Drive and Operate Machinery
Patients should be warned that the use of Modecate may impair their ability to perform activities requiring mental alertness or physical co-ordination (eg. operating machinery, driving a motor vehicle).

Abrupt Withdrawal
In general, phenothiazines do not produce physical or psychological 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 antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Phenothiazine antipsychotics elevate prolactin levels; the elevation persists during chronic administration. An increase in mammary neoplasms has been found in rodents after chronic administration of phenothiazine antipsychotics Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain antipsychotic drugs.

The effect of phenothiazines on human fertility is not known; however, phenothiazines have been found to depress spermatogenesis in animals at doses greatly exceeding the human dose.

Use in Pregnancy (Category C)
When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the newborn infant.

The safe use of Modecate during pregnancy has not been established. Usage of phenothiazines near term or during labour may result in significant maternal hypotension or other events (eg. neonatal jaundice, neonatal hypo or hyperreflexia or extrapyramidal symptoms) that may be detrimental to the health of the mother or the neonate.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including **MODECATE)** during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market 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 additional medical treatment
or monitoring.

MODECATE should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Use in Lactation
Phenothiazines are excreted into breast milk. In addition, phenothiazines may induce hyperprolactinaemia and galactorrhoea and thus, may interfere with proper lactation. Breastfeeding is therefore not recommended during treatment with Modecate.

Use in Children
Since there is no adequate experience in children who have received this drug, safety and efficacy in children have not been established.

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, perhaps because of differing pharmacodynamic factors. Antipsychotic drugs may be used in elderly patients who exhibit core psychotic symptoms such as delusions and hallucinations. Doses in the lower range (1/4 to 1/3 of those in younger adults) should be sufficient for most elderly patients. Since the elderly appear to be more susceptible to orthostatic hypotension, anticholinergic, sedative and extrapyramidal side effects, patients should be observed closely. Response should be monitored and dose adjusted. If an increase is necessary, doses should be gradually increased.

Interactions
Fluphenazine is a dopamine receptor blocker with anticholinergic, sedative, anti-*a*-adrenergic and extrapyramidal effects. Fluphenazine is metabolised by cytochrome P (CYP) 450 2D6 and is itself an inhibitor of this drug metabolising enzyme. The plasma concentrations and the effects of Modecate 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.

Alcohol
Potentiation of the effects of alcohol may occur with the use of this drug.

CNS Depressants/Analgesics
The patient's response to other CNS depressants such as hypnotics, tramadol, sedatives or strong analgesics may be exaggerated while taking Modecate. Combined use with narcotic analgesics may cause hypotension as well as CNS or respiratory depression.

Barbiturates may induce the hepatic metabolism of Modecate, possibly resulting in decreased antipsychotic effect. Due to a lowering of seizure threshold by Modecate, adequate barbiturate therapy should be maintained if administered for anticonvulsant purposes, when Modecate is added.

Tricyclic Antidepressants
High doses of tricyclics antidepressants may increase the plasma levels of Modecate. Modecate can also impair the metabolism of tricyclic antidepressants. Serum concentrations of both the tricyclic antidepressants and fluphenazine are increased. Sedative, CNS and antimuscarinic effects may be potentiated or prolonged. Tricyclic antidepressants may also cause additive cardiac effects (eg. QT prolongation) in some cases.

Lithium
Modecate interacts with lithium thereby predisposing the patient to adverse reactions, such as severe extrapyramidal side effects or neurotoxicity. It is hypothesised that the phenothiazines might increase lithium influx in red blood cells and that the enhanced concentrations of lithium in the tissue may possibly be responsible for the neurotoxic effects. Nausea and vomiting, early indications of lithium toxicity, may be masked by the antiemetic effect of fluphenazine. Lithium may also decrease serum Modecate levels, possibly by delaying gastric emptying, which may increase fluphenazine metabolism. If lithium is prescribed with Modecate, lithium concentrations and patient response should be carefully monitored. Lithium concentrations alone may not be indicative of possible neurotoxicity.

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

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

Diuretic-induced hypokalaemia may potentiate phenothiazine-induced cardiotoxicity.

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

Antihypertensives
Modecate may reverse the blood-pressure lowering effects of adrenergic-blocking agents such as guanethidine and clonidine by decreasing the uptake of these drugs into the adrenergic neuron. Patients should be monitored for maintenance of appropriate clinical response to antihypertensive therapy if Modecate is added; these combinations should be avoided whenever possible.

Clonidine may decrease the antipsychotic acitivity of phenothiazines.

Beta Blockers
Plasma levels of Modecate and the beta blocker may be increased as these two drugs mutually inhibit the liver metabolism of each other. Concurrent use of beta blockers, possibly including ophthalmic preparations, with Modecate may therefore result in an increased plasma concentration of each drug, resulting in additive hypotensive effects, irreversible retinopathy, cardiac arrhythmias and tardive dyskinesia. Dosage reduction of both drugs is recommended. Beta blockers with greater renal elimination (eg. atenolol) are less likely to have an interaction with phenothiazines.

Adrenaline and Other Sympathomimetics
Modecate may antagonize the action of adrenaline and other sympathomimetics by the alpha adrenergic blocking activity of fluphenazine. This blockage can lead to severe hypotension with postural syncope, tachycardia and potentially, myocardial infarction (see **PRECAUTIONS – Other Medical Conditions**).

Anti-Parkinsonian Drugs
Modecate may inhibit the clinical anti-Parkinson response to levodopa, pergolide, pramipexole, ropinirole or bromocriptine therapy by blocking dopamine receptors in the brain. Medications like entacaopone, tolcapone, pramipexole and ropinirole may also cause additive drowsiness when combined with fluphenazine. Dopamine agonists may also induce or exacerbate psychotic symptoms. In general, phenothiazines should be avoided in patients requiring therapy for Parkinson's disease (see **PRECAUTIONS – Other Medical Conditions**).

Anticholinergics/Antimuscarinics
Cholinergic blockade may be exaggerated when Modecate 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 is used with other anticholinergic or antimuscarinic drugs. Drugs with an anticholinergic activity include, but are not limited to, atropine, antiparkinson agents, butyrophenones, sedating H_1 blockers, tricyclic antidepressants, other phenothiazines and agents used to manage extrapyramidal side effects, such as benserazide.

Anticonvulsants
Concomitant use of Modecate with anticonvulsants may lower the seizure threshold and can increase CNS depression. Dosage adjustments of anticonvulsants may be necessary. Modecate may inhibit phenytoin metabolism, leading to phenytoin toxicity. Carbamazepine is a potent inducer of the CYP450 mixed-function hepatic oxidase system and can reduce plasma

concentrations of phenothiazines by 47% or more. If Modecate and carbamazepine must be used together, dosage adjustments of Modecate may be required.

Anticoagulants
Modecate 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 Modecate through inhibition of CYP450.

Amphetamine/Anorectic Agents
Amphetamines and Modecate can interfere with the therapeutic actions of each other. Amphetamines appear to aggravate psychotic symptoms. Modecate blocks dopamine and noradrenaline reuptake and thus decreases the anorectic and CNS stimulatory effects of the amphetamines.

Drugs that Prolong QT Interval
Phenothiazines have been associated with orthostatic hypotension and a risk of QT prolongation and/or torsades de pointes, particularly at higher doses. Drugs that prolong the QT interval could lead to additive orthostatic hypotension and/or prolonged QT syndrome and torsade de pointes when combined with Modecate and generally should be avoided.

Antipsychotic Drugs, Metoclopramide or Fluoxetine
Concomitant use of Modecate with other antipsychotic drugs (eg. other phenothiazines, butyrophenones including haloperidol) and metoclopramide or fluoxetine may increase the risk of extrapyramidal reactions.

SSRIs
Concomitant use of Modecate with SSRIs, including bupropion, may result in increases in Modecate concentrations as SSRIs and bupropion impair the metabolism of the CYP2D6 pathway.

Monoamine Oxidase Inhibitors
Due to the potential for additive CNS and cardiovascular effects, MAOIs and Modecate should be used together cautiously.

Drugs that Lower Seizure Threshold
Concomitant administration of Modecate with drugs that lower the seizure threshold (eg. antidepressants, other typical and atypical antipsychotics, aminophylline, bupropion, propofol, tramadol and narcotic analgesics, cyclosporin, large IV doses of antibiotics) may increase seizure risk.

Tobacco Smoke
Tobacco smoke contains polycyclic aromatic hydrocarbons that induce hepatic CYP450 microsomal enzymes. There is some evidence to suggest that tobacco smoke accelerates the metabolism of the phenothiazine antipsychotics. Because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, the sudden cessation of tobacco smoking may result in a reduced clearance of these antipsychotics, despite the initiation of a nicotine replacement product. Monitor patients carefully when changes in smoking status occur.

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

Anti-thyroid Agents
Concurrent use of anti-thyroid agents with Modecate may increase the risk of agranulocytosis.

Ototoxic Agents
The antiemetic effect of fluphenazine may effectively mask vestibular symptoms (eg. dizziness, tinnitus or vertigo) associated with ototoxicity induced by various medications such as the aminoglycosides.

Bromocriptine and Cabergoline
Due to antagonistic mechanisms of actions, Modecate may limit the ability of bromocriptine or cabergoline to lower serum prolactin concentrations. The combination should be avoided where possible. Bromocriptine and cabergoline do not appear to interfere with the antipsychotic effects of Modecate if these are added to stable antipsychotic regimens.

Laboratory Tests
Urinary metabolites of phenothiazines may cause the urine to darken and result in false positive test results for bilirubin, amylase, uroporphrins, porphobilinogens and 5-hydroxyindoleacetic acid. False positive test results for phenylketonuria (PKU) may also occur during phenothiazine use. Phenothiazines may interfere with metyrapone tests by reducing adrenocorticotrophin hormone (ACTH) secretion.

Phenothiazines may produce false positive or false negative pregnancy tests depending on the test used. Phenothiazines may blunt response to gonadorelin by increasing serum prolactin concentrations.

ADVERSE REACTIONS

Central Nervous System
The side effects most frequently reported with Modecate, as with other phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Most often these extrapyramidal symptoms are reversible; however, they may be persistent. The frequency of such reactions is related in part to chemical structure: one can expect a higher incidence with Modecate than with less potent piperazine derivatives or with straight-chain phenothiazines such as chlorpromazine. With any given phenothiazine derivative, the incidence and severity of such reactions depend more on individual patient sensitivity than on other factors, but dosage level and patient age are

also determinants. Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions can usually be controlled by administration of antiparkinsonian drugs such as benztropine mesylate and by subsequent reduction in dosage.

Dystonic reactions such as acute distressing spasm of muscles in the face, neck, eyes, tongue and back usually occur within 24 hours of an injection. This requires immediate administration of an anticholinergic (eg. benztropine or benzhexol) which will need to be continued orally on a regular basis for a few days to prevent recurrence. Young males are usually the patients at greatest risk. Laryngeal dystonia is rare, but potentially fatal.

Parkinsonism effects occur frequently to some degree and more so in older patients. These occur usually 2 to 5 days after an injection or after a dosage increase but may also develop on withdrawal. Early detection is important, therefore the patient's motor neurological system should be examined.

Anti-Parkinsonism drugs should not be prescribed routinely, because of the possible risks of aggravating anticholinergic side effects or precipitating toxic confusional states or of impairing therapeutic efficacy.

Tardive Dyskinesia
As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients, patients with organic brain damage and females. Other risk factors include affective disorder and schizophrenia characterised by negative symptoms. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterised by rhythmical involuntary movements of the tongue, face, mouth or jaw (eg: protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop. (See **PRECAUTIONS – Tardive Dyskinesia**)

To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of Modecate should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder.

Tardive dyskinesia appears most commonly after several months of treatment. It does not respond to antimuscarinics and is made worse by stopping treatment.

Neuroleptic Malignant Syndrome
Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. Leukocytosis, fever, elevated creatine kinase, liver function abnormalities,

and acute renal failure may also occur with NMS.(See **PRECAUTIONS – Neuroleptic Malignant Syndrome**)

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 dosages of fluphenazine far in excess of the recommended amounts. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered. Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement or bizarre dreams. Alterations in electroencephalographic tracings or cerebrospinal fluid proteins may occur; cerebral oedema may rarely occur.

Autonomic Nervous System
Hypertension and fluctuations in blood pressure have been reported with fluphenazine enanthate. Hypotension has rarely presented a problem with Modecate. However, patients with phaeochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency, or who are elderly or alcoholic, appear to be particularly prone to hypotensive reactions with phenothiazine compounds and should therefore be observed closely when the drug is administered. If severe hypotension should occur, supportive measures including the use of intravenous vasopressor drugs should be instituted immediately. Adrenaline should not be used since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.

Autonomic reactions including nausea, fainting, gastric irritation 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, faecal impaction, paralytic ileus, tachycardia, or nasal congestion.

The occasional increase in activity resulting from treatment may augment the severity of pain in angina pectoris patients. Such patients should be observed carefully and Modecate withdrawn if necessary.

Behavioural
Increased aggressiveness, activation of psychotic symptoms, catatonic and toxic confusional states have also been reported with the phenothiazines.

Metabolic and Endocrine
Weight changes, peripheral oedema, hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion, galactorrhoea, abnormal lactation, gynaecomastia, menstrual irregularities, false results on pregnancy tests, impotence, priapism, inhibition of ejaculation in men and increased libido in women have all been reported in association with various phenothiazines. Alterations may occur in blood glucose levels leading to loss of diabetic control

Allergic Reactions
Skin disorders such as itching, erythema multiforme, skin pigmentation, contact sensitivity, hypertrophic papillae of the tongue, urticaria, seborrhoea, photosensitivity, eczema and even

exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind. Asthma, laryngeal oedema and angioneurotic oedema may occur.

A syndrome representing systemic lupus erythematous has been reported very rarely.

Haematological
Routine blood counts are advisable during therapy since blood dyscrasias including leucopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Aplastic and haemolytic anaemias have also been reported. Potentially fatal agranulocytosis has occasionally been reported. Most cases have occurred within 4 to 10 weeks of starting treatment. Furthermore, if any soreness of the mouth, gums or throat, fever, or any symptoms of upper respiratory infection occur and confirmatory leucocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

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. Alterations in liver function tests and hepatitis have been reported in patients receiving fluphenazine.

Special Senses
In some patients, reactions have included blurred vision, mydriasis, corneal opacity, pigmentation of the eyes and glaucoma. Phenothiazines may induce a pigmentary retinopathy which is dependent on both the dose and duration of treatment. Deposition of particulate matter in the lens and cornea has occurred with some phenothiazines. Modecate therapy should be discontinued if corneal, retinal or lens changes are noticed. Blurred vision, defective colour vision and night blindness are early symptoms of pigmentary retinopathy and may be reversible if detected and the phenothiazine discontinued in the early stages. Patients expected to require higher doses of phenothiazines for prolonged periods should have complete eye examinations at baseline and every six to 12 months thereafter.

Others
Sudden, unexpected and unexplained deaths have been reported in hospitalised psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behaviour patterns shortly before death. Other possible causes for these deaths include cardiac arrhythmias or asphyxia due to suppression of the cough and gag reflexes. Fever, vomiting, systemic lupus erythematosus-like syndrome and altered EKG tracings have been reported with long-term use; skin pigmentation, and lens and corneal opacities have occurred. Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs.

Alterations in the pattern of proteins in the cerebrospinal fluid may also occur. The occurrence of cerebral oedema and hypotension, severe enough to cause fatal cardiac arrest, has been reported, as have alterations in both the electroencephalogram (EEG) and

electrocardiogram(ECG). ECG changes may include prolongation of the QT interval and T wave changes. These effects have been reported to proceed serious arrhythmias, including torsade de pointes, which have also occurred after phenothiazine overdose. Potentiation of central nervous system depressants may occasionally be severe enough to cause management problems.

Body temperature regulation is impaired and may result in hypo-or hyperthermia depending on the environment. Patients with hypothyroidism may be particularly susceptible to hypothermia.

Vomiting has also occurred with phenothiazine derivatives.

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

DOSAGE AND ADMINISTRATION

Modecate is not intended for short-term therapy (less than 3 months). Modecate is given intramuscularly. A dry syringe and needle of at least 21 gauge should be used. Use of a wet needle or syringe may cause the solution to become cloudy. Each Modecate ampoule is for one dose in one patient only. Discard any remaining contents.

To begin therapy the following regimens are suggested. For most patients a dose of 12.5 to 25mg (0.5 to 1mL) may be given to initiate therapy.

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. Subsequent injections and the dosage interval are determined in accordance with the patient's response. When administered as maintenance therapy, a single injection may be effective in controlling schizophrenic symptoms up to 4 weeks or longer. The response to a single dose has been found to last as long as 6 weeks in a few patients on maintenance therapy.

It may be advisable that patients who have had no history of taking phenothiazines should be treated initially with a shorter acting form of fluphenazine before administering the decanoate, to determine the patient's response to fluphenazine and to establish appropriate dosage.

No precise formula can be given to convert from short-acting forms of this drug to use of Modecate; however, a controlled multi-centre study in patients receiving oral doses from 5 to 60mg fluphenazine HCl daily, showed that 20mg fluphenazine HCl daily was equivalent to 25mg (1mL) Modecate every three weeks. This represents an approximate conversion ratio of 0.5mL (12.5mg) of fluphenazine decanoate every three weeks for every 10mg of fluphenazine HCl daily.

Severely agitated patients may be treated initially with a rapid acting phenothiazine compound. When acute symptoms have subsided, Modecate 25mg (1mL) may be administered; subsequent dosage is adjusted as necessary.

In poor risk patients (those with known hypersensitivity to phenothiazines, or with disorders that predispose to undue reactions) therapy may be initiated cautiously with oral fluphenazine

hydrochloride. When the pharmacological 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. The optimal amount of the drug and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug. Dosage should not exceed 100mg. If doses greater than 50mg are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5mg.

Elderly Patients
Doses in the lower range (1/4 to 1/3 of those in younger adults) may be sufficient for most elderly patients. Response should be monitored. If necessary, dosage should be gradually increased.

OVERDOSAGE

Symptoms
Due to its long duration of action, manifestations of overdose with Modecate Injection may be prolonged.

In general, the symptoms of overdose are extensions of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. CNS depression progressing to coma with areflexia may occur, as can cardiac arrhythmias. Restlessness, confusion and excitement may occur with early or mild intoxication.

Treatment
The drug should be withdrawn and the symptoms of overdose treated supportively. A patent airway should be established by the use of an oropharyngeal airway or endotracheal tube and respiratory depression may need to be managed by artificial respiration. ECG and vital signs should be monitored, and body temperature and respiratory function should be maintained.

If severe hypotension should occur, supportive measures, including the use of intravenous vasopressor drugs should be instituted immediately. Noradrenaline acid tartrate is the most suitable drug for this purpose; adrenaline should not be used, since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure. If severe extrapyramidal reactions occur, antiparkinson medication should be administered, 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. Haemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis are ineffective in phenothiazine poisoning.

PRESENTATION

Injection (in sesame oil with 1.5% benzyl alcohol), 25mg/mL, 0.5mL, 1mL, 2mL (ampoules): 5's.

Storage Recommendations

Do not store above 25 degrees C. Do not refrigerate or freeze. Protect from direct sunlight. Parenteral drug products should be inspected visually for particles and discolouration prior to administration, whenever solution and container permit.

NAME AND ADDRESS OF THE SPONSOR

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DATE OF MOST RECENT AMENDMENT

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