PRODUCT MONOGRAPH

[Pr] Haloperidol Decanoate Injection
(Haloperidol Decanoate Injection)
50 mg and 100 mg haloperidol/mL

ANTIPSYCHOTIC AGENT

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

Date of Preparation: July 16, 2014

Submission Control No: 175361

PRODUCT MONOGRAPH

[Pr] Haloperidol Decanoate Injection
(Haloperidol Decanoate Injection)
50 mg and 100 mg haloperidol/mL

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Haloperidol decanoate, an ester derivative of haloperidol obtained from condensation of haloperidol with decanoic acid possesses the antipsychotic properties of haloperidol. When it is administered as an intramuscular (i.m.) depot in sesame oil, esterases present in blood and tissues hydrolyze haloperidol decanoate to provide a slow release of the active neuroleptic haloperidol from the depot into the systemic circulation. The onset of action occurs within a few days after injection and the therapeutic effect continues for 2 to 4 weeks, although adequate control is frequently maintained with 1 injection every 4 weeks. Careful supervision is required throughout treatment due to the variations in individual patient response.

Haloperidol decanoate possesses antiemetic properties; it has a marked tendency to provoke extrapyramidal effects and has relatively weak alpha-adrenolytic properties. It may also exhibit hypothermic and anorexiant effects and potentiate the action of barbiturates, general anesthetics, and other CNS depressant drugs.

As with other neuroleptics, the mechanism of action of haloperidol decanoate has not been entirely elucidated, but has been attributed to the inhibition of the transport mechanism of cerebral monoamines by haloperidol, particularly by blocking the impulse transmission in dopaminergic neurons.

Pharmacokinetics

The pharmacokinetics were studied in chronic psychotic patients receiving monthly injections for up to 2 years. The initial dose was based on the observation that the bioavailability of oral haloperidol is 60 to 70%, corresponding to a monthly dose of haloperidol decanoate of about 20 times the daily oral dose. Patients were switched abruptly from their previous oral maintenance

medication and plasma levels of haloperidol were measured at fixed intervals after injections. At the end of the first 4-week period, plasma haloperidol levels were similar to steady state levels attained with oral administration; however, the levels immediately following injection were considerably higher. Accumulation of plasma levels was observed for the first 3 to 6 months, after which a steady state was reached at levels about 2 to 3 times higher than in the first month of treatment.

Depending on the dose (25 to 400 mg equivalents of haloperidol), at the end of injection period steady state levels ranged from about 1 to 13 ng/mL; this range of blood levels is similar to that found in patients administered oral haloperidol.

Plasma haloperidol levels were also measured in patients who first received haloperidol decanoate in the 50 mg eq/mL concentration and subsequently were given the 100 mg eq/mL concentration. No significant differences in plasma levels were observed.

The half-life has been estimated at about 3 weeks. Haloperidol is metabolized in the liver and excreted in urine and feces.

INDICATIONS AND CLINICAL USE

Haloperidol decanoate is of value in the management of manifestations of chronic schizophrenia.

CONTRAINDICATIONS

Haloperidol decanoate is contraindicated in comatose states and in the presence of CNS depression due to alcohol or other depressant drugs. It is also contraindicated in patients with severe depressive states, previous spastic diseases, lesions of the basal ganglia and in Parkinson's syndrome, except in the case of dyskinesias due to levodopa treatment. It should not be used in patients known to be sensitive to the drug, nor in senile patients with pre-existing Parkinson-like symptoms.

Children

Safety and effectiveness in children have not been established; therefore, haloperidol decanoate is contraindicated in this age group.

Pregnancy and Lactation

Haloperidol decanoate has shown no significant increase in fetal anomalies in large population studies. There have been isolated case reports of birth defects following fetal exposure to haloperidol decanoate in combination with other drugs. It should, therefore, not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the physician, the expected benefits of the drug outweigh the potential hazard to the fetus or child. Haloperidol is excreted in breast milk. Extrapyramidal symptoms have been observed in breast-fed infants of haloperidol decanoate treated women.

WARNINGS

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including haloperidol decanoate. Since QT-prolongation has been observed during haloperidol decanoate treatment, it is advised to be cautious in patients with QT-prolonging conditions (QT-syndrome, hypokalemia, drugs known to prolong QT).

Tardive Dyskinesia

Tardive dyskinesia is known to occur in patients treated with neuroleptics with antipsychotic properties and other drugs with substantial neuroleptic activity. Although the dyskinetic syndrome may remit partially or completely if the medication is withdrawn, it is irreversible in some patients. At the present time there is uncertainty as to whether neuroleptic drugs differ in their potential to cause tardive dyskinesia.

Since there is a significant prevalence in this syndrome associated with the use of neuroleptic drugs, and since there is no known effective treatment, chronic use of these drugs should generally be restricted to patients for whom neuroleptics are known to be effective and for whom there is no alternative therapy available with better risk acceptability. If manifestations of tardive dyskinesia are detected during the use of a neuroleptic, the drug should be discontinued.

The risk of a patient developing tardive dyskinesia and of the syndrome becoming irreversible appear to increase with the duration of treatment and the total amount of drugs administered, although, in some instances, tardive dyskinesia may develop after relatively short periods of treatment at low doses. The risk of developing tardive dyskinesia may, therefore, be minimized by reducing the dose of the neuroleptic drug used and its duration of administration, consistent with the effective management of the patient's condition. Continued use of neuroleptics should be periodically reassessed.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described under Tardive Dyskinesia, except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but, until further evidence becomes available, it seems reasonable to withdraw gradually use of antipsychotic drugs.

In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, brain stem disorder, acute brain syndrome and coma. Most of these symptoms were reversible; it remains unclear whether this represents a distinct clinical entity. Nonetheless, it is advised that in patients who are treated concomitantly with lithium and haloperidol, therapy should be stopped immediately if such symptoms occur.

Elderly or debilitated patients receiving the drug should be carefully observed for lethargy and decreased sensation of thirst due to central inhibition, which might lead to dehydration and reduced pulmonary ventilation, and could result in complications such as terminal bronchopneumonia.

Occupational Hazards

Although haloperidol is a relatively nonsedating neuroleptic, sedation may occur in some patients. Therefore physicians should be aware of this possibility and caution patients about the danger of participating in activities requiring complete mental alertness, judgment, and physical coordination, such as driving and operating dangerous machinery.

Haloperidol may prolong the hypnotic action of barbiturates and may potentiate the effects of alcohol and other CNS depressant drugs, such as anesthetics and narcotics; caution should, therefore, be exercised when it is used with agents of this type. Adjustments in their dosage may be required.

Endocrine and Metabolism

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

body weight.

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

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

PRECAUTIONS

Administration to patients with severe cardiac involvement should be guarded, despite the fact that haloperidol is well tolerated by patients with cardiac insufficiency and that it has been used with favorable results to maintain the cardiovascular function of patients with excitive crises. In very rare instances, it has been felt that haloperidol was contributory to the precipitation of attacks in angina-prone patients. Moderate hypotension may occur with parenteral administration or excessive oral doses of haloperidol; however, vertigo and syncope occur only rarely.

It has been reported that seizures can be triggered by haloperidol decanoate. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g., alcohol withdrawal and brain damage).

As with other antipsychotic agents, haloperidol should be administered cautiously to patients with severe impairment of liver or kidney function, and to patients with known allergies or history of allergies to other neuroleptic drugs. Caution is also advised in patients with pheochromocytoma and conditions predisposing to epilepsy, such as alcohol withdrawal and brain damage.

Haloperidol has lowered the level of cholesterol in the serum and liver of monkeys. An accumulation of desmosterol has been observed in the serum of rats given repeated high doses (10 mg/kg) of haloperidol. In man, mild transient decreases in serum cholesterol were reported in preliminary studies. However, in a study involving a group of schizophrenic patients on extended medication, significant lowering of serum cholesterol was not observed with haloperidol, and there was no accumulation of desmosterol or 7-dehydro-cholesterol. A significant lowering of cholesterol together with an accumulation of another sterol (possibly 7-dehydrocholesterol) has been reported in patients receiving a chemically related drug

(trifluperidol) and skin and eye changes (ichthyosis and cataracts) have occurred clinically with another butyrophenone derivative. Skin and eye changes have not been observed in patients receiving haloperidol. However, it is advisable that all patients receiving haloperidol for a prolonged period of time be carefully observed for any changes in the skin and eyes. If such changes are seen, the drug should be discontinued promptly.

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 haloperidol and then periodically throughout treatment.

Drug Interactions

Haloperidol has been reported to interfere with the anticoagulant properties of phenindione in an isolated case, and the possibility should be kept in mind of a similar effect occurring when this product is used together with anticoagulants.

Haloperidol may antagonize the action of epinephrine and other sympathomimetic agents and reverse the blood pressure-lowering effects of adrenergic-blocking agents, such as guanethidine.

Enhanced CNS effects have been reported when haloperidol is used in combination with methyldopa. Haloperidol inhibits the metabolization of tricyclic antidepressants, thereby increasing plasma levels of these drugs.

When prolonged treatment with enzyme-inducing drugs (such as carbamazepine, phenobarbital, rifampicin) is added to haloperidol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the haloperidol dose should be adjusted, when necessary. After stopping such drugs it will be necessary to reduce the dosage of haloperidol.

Haloperidol may impair the antiparkinson effects of levodopa. If concomitant antiparkinson medication is required, it may have to be continued for at least a couple of weeks after the last haloperidol injection due to the very long half-life of haloperidol decanoate.

The physician should keep in mind the possibility of an increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

The antiemetic action of haloperidol may obscure signs of toxicity due to overdosage of other drugs or mask the symptoms of some organic diseases, such as brain tumor or intestinal obstructions.

Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol.

Carcinogenicity studies in mice (18 months) and rats (24 months) showed a significant increase in mammary gland neoplasia and total tumor incidence in female mice at 1.25 and 5 mg/kg/day and in pituitary gland neoplasia in female mice at 5 mg/kg. A significant dose related increase in pituitary gland hyperplasia was observed in female rats at 1.25 and 5 mg/kg/day. The potential significance of these findings to man is not known.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, which are presumed to be linked to elevated prolactin levels, the clinical significance of elevated serum prolactin levels is unknown for most patients. 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: the available evidence is considered too limited to be conclusive at this time.

It is recommended that patients being considered for haloperidol decanoate therapy be initially put on oral haloperidol to exclude the possibility of an unexpected adverse sensitivity to haloperidol.

As with all antipsychotic agents, haloperidol decanoate should not be used alone where depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist.

In pharmacokinetic studies mild to moderately increased haloperidol decanoate levels have been reported when haloperidol was given concomitantly with the following drugs: quinidine, buspirone, fluoxetine. It may be necessary to reduce the haloperidol (decanoate) dosage.

Effects on Driving Ability and Use of Machinery

Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. Patients should be advised not to drive or operate machinery during treatment, until their susceptibility is known.

Special Populations, Pregnant Women

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

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

ADVERSE REACTIONS

Neurological effects are the most common.

Extrapyramidal Symptoms

In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. Headache, vertigo, and cerebral seizures have also been reported. The extrapyramidal reactions are usually dose-related in occurrence and severity and, as a rule, tend to subside when the dose is reduced or the drug is temporarily discontinued. However, considerable interpatient variability exists, and although some individuals may tolerate higher than average doses of haloperidol, severe extrapyramidal reactions, necessitating discontinuation of the drug, may occur at relatively low doses.

Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure.

Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g.;

protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. The manifestations may be permanent in some patients.

The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects

Insomnia, depressive reactions, and toxic confusional states are the more common effects encountered. Drowsiness, lethargy, stupor and catalepsy, confusion, restlessness, agitation, anxiety, euphoria, vertigo, grand mal seizures and exacerbation of psychotic symptoms, including hallucinations, have also been reported.

Cardiovascular

Tachycardia, hypertension and ECG changes including ventricular arrhythmias and/or prolongation of the QT interval and ECG pattern changes compatible with the polymorphous configurations of torsades de pointes have been reported. Hypotension has occurred, but severe orthostatic hypotension has not been reported. However, should it occur, supportive measures, including intravenous (i.v.) vasopressors, such as norepinephrine, may be required. **Epinephrine should not be used**; haloperidol decanoate may block the vasoconstrictor effects of this drug.

Autonomic

Dry mouth, blurred vision, urinary retention, incontinence, diaphoresis and priapism, erectile dysfunctions, peripheral edema, excessive perspiration or salivation, heartburn, and body temperature disregulation have been reported.

Allergic and Toxic

The overall incidence of significant hematologic changes in patients on haloperidol has been low. Occasionally there have been reports of mild and usually transient leukopenia and leukocytosis, decreases in blood cell counts, anemia, and a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported with the use of haloperidol, and

then only in association with other medication. Impairment of liver function (jaundice or hepatitis) has been reported rarely. One case of photosensitization is known and isolated cases of idiosyncratic cutaneous involvement have been observed.

Agranulocytosis and thrombocytopenia have rarely been reported with the use of haloperidol, and then only in association with other medication.

Endocrine

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinemia, which may cause galactorrhea, gynecomastia and oligo- or amenorrhea. Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, changes in blood sugar levels and very rare cases of Syndrome of Inappropriate ADH Secretion have been reported.

Gastrointestinal

Heartburn, nausea, vomiting, anorexia, weight loss, weight gain, constipation, diarrhea and hypersalivation have been reported.

Miscellaneous

Other untoward effects which may be encountered include peripheral edema, hypocholesterolemia, alopecia, laryngospasm, bronchospasm and increased depth of respiration and stasis pneumonia. Hyperammonemia has been reported in a 5 1/2 year old child with citrullinemia, and inherited disorder of ammonia excretion, following treatment with haloperidol.

Cases of sudden and unexpected death have been reported in association with the administration of haloperidol. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

Neuroleptic Malignant Syndrome

As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, generalized muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Hyperthermia is often an early sign of this syndrome. Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis),

and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of neuroleptic treatment.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms

In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: severe extrapyramidal reactions; hypotension; or sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reaction would be manifest by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively.

In extreme cases the patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QT-prolongation should be considered. (For further information regarding torsades de pointes, please refer to ADVERSE REACTIONS).

Treatment

Since there is no specific antidote, treatment is primarily supportive but gastric lavage or induction of emesis is advised (unless the patient is obtunded, comatose, or convulsing) followed by administration of activated charcoal. For comatose patients, a patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of i.v. fluids or plasma or concentrated albumin and vasopressor agents such as norepinephrine. **Epinephrine should not be used since it may cause profound hypotension in the presence of haloperidol**. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of QT

prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate antiarrhythmic measures.

DOSAGE AND ADMINISTRATION

Administer by deep i.m. injection, preferably in the gluteus maximus. **This drug is not for i.v. use**.

As a long-acting, depot neuroleptic, it has been found useful in the maintenance management of chronic schizophrenic patients who have been stabilized with short acting medication, and who might benefit from transfer to longer acting injectable therapy. The changeover to haloperidol decanoate should aim at maintaining a clinical outcome similar to or better than that obtained with previous therapy in patients who cannot be relied upon to take oral medication regularly.

It is suggested that previous antipsychotic medication be discontinued before instituting therapy with haloperidol decanoate. Continuous supervision is required during the initial period of dosage adjustment in order to minimize the risk of overdosage or insufficient suppression of psychotic symptoms before the next injection. Supplemental oral haloperidol may be required in diminishing dosage during this period.

The selection of the initial dose of haloperidol decanoate should be based on the patient's symptomatology and previous oral neuroleptic dosage. A ratio of 20:1 of haloperidol decanoate to oral haloperidol appears to produce comparable steady state plasma levels of haloperidol with both dosage forms. Control of psychotic symptoms, however, has also been achieved with doses based on lower ratios (10 to 15 times the daily maintenance dose of oral haloperidol). In order to reduce the possible occurrence of adverse effects, it is advisable to initiate therapy with haloperidol decanoate at lower doses and adjust the dose upwards as needed. There is limited experience with patients transferred to haloperidol decanoate from other oral neuroleptics. If such a transfer is deemed desirable, it is suggested that the patient be converted initially from the previous antipsychotic medication to oral haloperidol in order to exclude the possibility of an unexpected adverse sensitivity to haloperidol.

The average duration of action of haloperidol decanoate is 4 weeks. The frequency of administration and the dosage must, however, be individually determined for each patient. The dose should not be increased with the intent of prolonging the interval between injections beyond 4 weeks, since higher doses may increase the incidence of extrapyramidal symptoms and other

adverse effects. Occasionally, patients may require higher dosages and/or shorter injection intervals, such as 3 or even 2 weeks.

Clinical experience with haloperidol decanoate at doses greater than 300 mg has been limited and much lower doses are usually adequate to achieve symptom control. In order to minimize the possible occurrence of serious and potentially irreversible adverse effects, the lowest neuroleptic dosage should be used which is consistent with effective management of the patient.

After appropriate dosage adjustment is achieved, regular reassessment is considered essential to allow additional adjustments which will ensure that the lowest effective individual doses are used.

Geriatrics and Debilitated Patients

Lower initial doses and more gradual titration are recommended in elderly and debilitated patients.

Patients who require higher doses of haloperidol decanoate and/or those who complain of discomfort with a large injection volume may be administered haloperidol decanoate 100 mg eq/mL in preference to haloperidol decanoate 50 mg eq/mL.

As with all oily injections, it is important to ensure, by aspiration before injection, that inadvertent intravascular injection does not occur.

A dry syringe and a dry 5 cm needle of 21 gauge should be used for patients with a normal amount of body fat. Obese patients should be injected with a 6.5 cm needle in order to ensure that the injection goes into muscle.

PHARMACEUTICAL INFORMATION

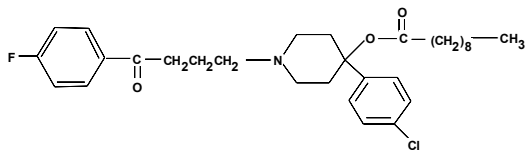
DRUG SUBSTANCE

Proper/Common Name: Haloperidol Decanoate

Chemical Name(s):

1) Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester;
2) Decanoic acid, ester with 4-[4-(p-chlorophenyl)-4-hydroxy-piperidino]-4′-fluorobutyrophenone.

Structural Formula:



Molecular Formula: $C_{31}H_{41}ClFNO_3$

Molecular Weight: 530.13

Description:

Haloperidol decanoate is a white to pale yellow powder. It is slightly soluble in water; and soluble in ethanol, ether, acetone and chloroform.

COMPOSITION

Each mL of Haloperidol Decanoate Injection contains haloperidol decanoate (equivalent to 50 mg or 100 mg haloperidol), and the following non-medicinal ingredients: benzyl alcohol (1.2% v/v as preservative), sesame oil (as vehicle).

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature 15-30ºC (59-86ºF). Do not refrigerate or freeze. Protect from light. Discard 28 days after initial puncture. Keep in carton until discarded.

AVAILABILITY OF DOSAGE FORMS

Haloperidol Decanoate Injection (haloperidol decanoate injection), 50 mg and 100 mg haloperidol/mL, is available in 1 mL single dose vials and 5 mL multiple dose vials.

PHARMACOLOGY

The pharmacological profile of haloperidol in laboratory animals resembles that of the phenothiazine antipsychotics. As with other neuroleptics, it reduces locomotor and exploratory behaviour (ambulation and "emotional" defecation) in rats at low doses and induces cataleptic immobility and palpebral ptosis at higher doses. Haloperidol is more potent than chlorpromazine in abolishing the righting reflex in mice (milligram potency two times that of chlorpromazine). It also depresses food consumption and weight increase in laboratory animals and has an epileptogenic effect at subtoxic dose levels. Haloperidol suppresses the conditioned avoidance response in the jumping box test (milligram potency 16 times that of chlorpromazine in rats). It blocks amphetamine-induced activity in rats and apomorphine-induced emesis in dogs (milligram potency 50 times that of chlorpromazine), but it is weaker than chlorpromazine in prolonging barbiturate sleeping time. It has relatively weak adrenolytic properties. Equal doses of haloperidol and chlorpromazine are required to produce significant hypotension in the cat and hypothermia in the rat. In dogs and cats it decreases the epinephrine-induced contractions of the nictitating membrane but is less effective against norepinephrine. It would appear from studies in the rabbit that the decreased responsiveness of the reticular formation produced by the drug may be more marked in the caudal portion of that area. Changes in the EEG activity produced by haloperidol are similar to those seen with phenothiazine derivatives.

The duration of the antiemetic activity of single intramuscular doses of haloperidol decanoate was studied in dogs. Protection against apomorphine-induced emesis in 50% of the dogs was obtained for 14 days with 0.63 mg/kg, for 28 days with 2.5 mg/kg, and for up to 56 days with 10 mg/kg.

In another study, 6 mg/kg of a 10% concentration of haloperidol decanoate protected 5/5 dogs for a mean of 49 days, while 2 mg/kg of the same concentration afforded protection for 29 days. The effectiveness of 6 mg/kg of a 5% concentration was more variable, and, on average, of shorter duration. The onset of antiemetic activity was usually more than 4, but less than 24 hours after administration. Slight to moderate decrease in motor activity was seen during the first few days.

A study in dogs exploring the relationship between the subcutaneous dose of haloperidol, the plasma concentration, and the antiemetic activity showed that all dogs in the study vomited when haloperidol plasma concentrations were below 1 ng/mL, while all were protected against vomiting at levels higher than 1 ng/mL. Pharmacokinetic studies in the dog show that the single dose of haloperidol decanoate required to maintain a level of at least 1 ng/mL over a period of 28 days is between 2 and 3.8 mg/kg. After repeated dosing, 1 mg/kg is almost, but not quite, sufficient to maintain a plasma level of 1 ng/mL for 28 days.

Pharmacokinetics

The pharmacokinetic profile of haloperidol decanoate in Beagle dogs was studied after both single and repeated administration at different dose levels. Haloperidol plasma levels were determined by radioimmunoassay.

After single doses (equivalent to 0.5, 1, 2, 4, and 8 mg haloperidol base/kg), plasma levels of haloperidol were maximal 4-11 days after dosing. At the lowest dose, detectable plasma levels were observed one hour after administration. Plasma levels decreased monophasically for the lower (0.5 and 1 mg/kg) and biphasically for the higher dose levels (2, 4 and 8 mg/kg), corresponding to half-life values of 12-20 days for the first phase and more than 40 days for the second phase.

After repeated administration of the equivalent of 1, 4 and 16 mg haloperidol base/kg at 4-week intervals for six months, haloperidol plasma levels were observed to peak 3-9 days after each dosing. Steady-state levels were reached after the third injection for the lowest dose and after the sixth injection for the two higher doses. Minimum steady-state levels were, respectively, 1.5, 2 and 3 times higher than plasma levels 4 weeks after the first dose. Steady state levels were dose related.

Tissue levels of haloperidol, three weeks after the seventh intramuscular dose of haloperidol decanoate, were highest in the liver and adrenals. Markedly lower levels were found in the brain, lung, kidney, fat and skeletal muscle. Tissue concentrations exceeded many times those found in plasma.

Receptor binding studies have demonstrated that the affinity of haloperidol decanoate for the neuroleptic receptors is negligible, indicating that haloperidol decanoate is a pro-drug which itself is not active but has to be transferred by enzymatic hydrolysis into the active drug haloperidol in order to achieve a pharmacological effect.

TOXICOLOGY

Acute Toxicity Studies

The intramuscular LD_{50} was estimated to be greater than 400 mg/kg in rats. Attempts to determine LD_{50} values were not successful since the maximum dose that could be injected without seepage was 400 mg/kg using the 50 mg eq/mL formulation and 800 mg/kg using the 100 eq/mL formulation.

Similar side effects were observed in rats dosed with either of the two drug formulations. These include decreased activity, relaxed palpebrae, unkempt appearance, chromorhinorrhea and hyperreactivity to touch. Chromodacryorrhea, hyperemia of the skin and paw pads, hunched posture, thin appearance, urine stained abdominal hair, diarrhea and lacrimation were also seen.

Subacute and Chronic Toxicity Studies

In a single dose irritation study, 0.4 mL haloperidol decanoate in 4 different concentrations (equivalent to 40, 50, 75 and 100 mg haloperidol base/mL) was administered intramuscularly to rabbits. Over a 14-day observation period, a slight local irritation in approximately half the injection sites was observed with all concentrations of the haloperidol decanoate solutions without dosage response. A control group receiving 25 mg/mL fluphenazine decanoate i.m., showed no local irritation.

In another intramuscular toxicity and irritation study, haloperidol decanoate was administered to rabbits weekly for 13 weeks at doses of 0, 5, 25 and 50 mg haloperidol base/kg. Effects attributed to drug treatment were injection site erythema (no apparent dosage relationship to incidence or severity), suppression of body weight gain (dose related) and decreased liver weight.

The toxicity of haloperidol decanoate was studied in dogs which received monthly i.m. injections of placebo or haloperidol decanoate (equivalent to 1, 4 and 16 mg haloperidol base/kg) for 6 months. All animals survived the study. No drug-related effects were observed except for an increase in and proliferation of basal cells in the prostates of high dose male dogs in comparison to the control animals.

During an 18-month evaluation in rats, haloperidol was administered in the diet in amounts that averaged 33.0, 14.5, 6.5, and 3.5, mg/kg/day. No gross or microscopic abnormalities were observed. At the end of the evaluation, however, there was a decrease in mean body weights and food consumption.

Two safety evaluations of haloperidol were conducted in dogs. In one study, the dogs received 2.0, 0.5 or 0 mg/kg/day for 6 months; in the other, 12.0, 6.0, 2.0 or 0 mg/kg/day for 12 months. No fatalities occurred in either study and none of the dogs in the 6-month evaluation exhibited any drug-related toxic effects (gross or microscopic). In the 12-month study, decreased weight gain, convulsions, tremors and emesis were observed at the higher dose levels only. Transient breast engorgement and lactation occurred in 6 of 12 female dogs but were not dose-related. Dose-related liver toxicity with hepatocellular changes were seen in dogs on the two highest doses and possibly at all dose levels. SGPT changes (increase) were reversible since they returned to normal in animals studied for one month after termination of dosing; liver sections from animals sacrificed at this time also indicated that cellular changes had returned toward normal.

Reproductive Studies

When haloperidol was administered to rats (0.6 - 3.0 mg/kg), rabbits (1.0 and 6.0 mg/kg) and dogs (1.0 - 4.0 mg/kg), the offspring of each of these species did not exhibit a greater incidence of teratologic effects than was observed in the respective control groups. In rats receiving amounts of the drug (4.0 mg/kg) large enough to produce marked CNS depression, increased delivery time was noted. Available data suggest that, in rats, large oral doses (1.9 mg/kg) may reduce libido, and that larger i.v. doses (3.0 mg/kg) may decrease implantation. An increased incidence of fetal resorptions was observed in rabbits receiving 6.0 mg/kg orally; however, at 1.0 mg/kg orally this effect was not observed.

Carcinogenicity Studies

Rats were given haloperidol as a drug/diet mixture at dosage levels of 0, 0.31, 1.25 and 5.0 mg/kg/day for 24 months. The survival rate was less than optimal in all dose groups, reducing the number of rats at risk.

Body weight gain was decreased in both male and female rats at the mid and high dose levels, and a temporary decrease also occurred in females at the low dose level. No drug or dose-related macroscopic lesions were observed in male rats. In female rats, an increased incidence of stimulation of the mammary glands was noted at the high dose.

Histopathological observations occurring at increased incidence in treated males included spleen parenchymal and follicular pigmentation at 5.0 mg/kg and mammary gland development at 5.0 and 1.25 mg/kg. Significant changes in females included an increase in pituitary gland hyperplasia and spleen parenchymal pigmentation at 5.0 and 1.25 mg/kg, and an increase in

spleen follicular pigmentation, mammary gland development and parenchymal pigmentation at 5.0 mg/kg.

In an 18-month carcinogenicity study in mice, haloperidol was mixed with the animals' normal daily diet at dosage levels of 0, 0.31, 1.25 and 5.0 mg/kg/day. Clinical observations included an increased incidence of subcutaneous masses at 5.0 and 1.25 mg/kg in female and a sedative effect in both male and female mice at the 5.0 mg/kg dose level.

Observations at necropsy revealed a number of drug-and dose-related changes. In female mice, there was an increased incidence of stimulation of the mammary glands and swelling of pituitary glands, often with hemorrhagic changes, at the 5.0 and 1.25 mg/kg dose levels. Other gross findings, not dose-related, included an increased incidence of anemia in males at 0.31 mg/kg, an increased incidence of obesity in females at 0.31 mg/kg, and an increased incidence of swollen spleen in females at 1.25 mg/kg.

Neoplastic changes included dose-dependent increases in the incidence of mammary gland carcinoma and pituitary gland adenoma in females at 5.0 and 1.25 mg/kg.

Other histopathological changes occurring at increased incidence in treated mice were also restricted to females. These were mammary gland inflammatory cell infiltration and metaplasia at 5.0 and 1.25 mg/kg, and secretion, fibrosis and hyperplasia at 5.0 mg/kg; pituitary gland ectasia at 5.0 and 1.25 mg/kg and, hyperplasia at 5.0 mg/kg; myelopoiesis of the lymph nodes at 5.0 mg/kg and myelopoiesis of the adrenal gland and dilated tubules of the kidney at 1.25 mg/kg.

The mammary and pituitary changes are thought to be related to the known enhancement of prolactin release and synthesis occurring as a result of dopamine antagonism.

BIBLIOGRAPHY

1) Ban TA, Ceskova E. Long-acting antipsychotic drugs. Psychopharmacol Bull 1980; 16(4): 6-13.

2) Chouinard G, et al: A double-blind, controlled clinical trial of haloperidol decanoate and fluphenazine decanoate in the maintenance treatment of schizophrenia. Psychopharmacol Bull 1984; 20: 108-109.

3) Cressman WA, Bianchine JR, Slotnick VB, Johnson PC, Plostnieks J. Plasma level profile of haloperidol in man following intramuscular administration. Eur J Clin Pharm 1974; 7: 99.

4) Deberdt R, Elens P, Berghmans W, Heykants J, Woestenborghs R, Driesens F, Reyntjens A, Van Wijngaarden I. Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plama levels. Acta Psychiat Scand 1980; 62: 356-363.

5) De Buck RP, et al: Theoretical and practical importance of plasma levels of haloperidol. Correlations with clinical and computerized EEG data. Prog Neuro-Psychopharmacol 1981; 5: 499-502.

6) Forsman A, Ohman R. Applied pharmacokinetics of haloperidol. Man Curr Ther Res 1977; 21: 396-411.

7) Haloperidol in psychiatry. The Medical Letter 1975; Jan. 31, 17(3).

8) Holley FO, Magliozzi JR, Stanski DR, Lombrozo L, Hollister LE. Haloperidol kinetics after oral and intravenous doses. Clin Pharmacol & Therap 1983; 33(4): 477-484.

9) Nair NPV, et al. A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: Efficacy, safety, and dosage equivalence. J Clin Psychopharmacol 1986; 6(1): 30S-37S.

10) Reyntjens AJM, et al: Pharmacokinetics of haloperidol decanoate. A 2-year follow-up. Int Pharmacopsychiat 1982; 17: 238-246.

11) Roose K. Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. Acta Psychiat Belg 1982; 2: 216-223.

12) Suy E, Woestenborghs R, Heykants J. Bioavailability and clinical effect of two different concentrations of haloperidol decanoate. Curr Therap Res 1982; 31(6): 982-991.

13) Viukari M, Salo H, Lamminsivu U, Grodin A. Tolerance and serum levels of haloperidol during parenteral and oral haloperidol treatment in geriatric patients. Acta Psychiat Scand 1982; 65: 301-308.

14) Youssef HA. A one-year study of haloperidol decanoate in schizophrenic patients. Curr Therap Res 1982; 31(6): 976-981.

15) Zissis NP, Psaras M, Lyketsos G. Haloperidol decanoate, a new long-acting antipsychotic, in chronic schizophrenics: Double-blind comparison with placebo. Curr Therap Res 1982; 31(4): 650-655.

16) CPS Monograph. Haldol® LA (Haloperidol Decanoate) - Antipsychotic. IN: Gillis MC, Welbanks L, Bergeron D, et al, eds. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, Ottawa, 1998; pp. 688-689.

17) Product Monograph. Haldol® LA (Haloperidol Decanoate) - Antipsychotic Agent. McNeil Pharmaceutical (Canada) Ltd., Stouffville, Ontario, November 14, 1988.

18) Product Monograph. APO-HALOPERIDOL LA Injectable (Haloperidol Decanoate Injection) – Antipsychotic Agent. Apotex Inc., Weston, Ontario, October 17, 2011; Control No.: 148961

PART III: CONSUMER INFORMATION

[Pr] Haloperidol Decanoate Injection (haloperidol decanoate injection)
50 mg/mL and 100 mg/mL

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

ABOUT THIS MEDICATION

What the medication is used for:

This medication is used for the management of manifestations of chronic schizophrenia.

What it does:

Haloperidol Decanoate Injection is an antipsychotic medication which affects chemicals in the brain that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how Haloperidol Decanoate Injection works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:

You should not use Haloperidol Decanoate Injection if you have:

- An allergy to haloperidol, to any of its ingredients or to phenothiazines
- A medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- A severe heart or blood vessel disorder
- Severe kidney problems
- Had brain damage
- Liver disease
- A blood cell disorder such as anemia, low white blood cell counts, or low platelets
- Drowsiness, slow breathing, weak pulse
- Decreased alertness caused by taking certain medications or drinking alcohol
- You are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)

What the medicinal ingredient is:

Haloperidol decanoate

What the nonmedicinal ingredients are:

Haloperidol Decanoate Injection contains the following non-medicinal ingredients: benzyl alcohol (1.2% as preservative) and sesame oil (as vehicle)

What dosage forms it comes in:

Haloperidol Decanoate Injection (haloperidol decanoate injection) 50 mg/mL and 100 mg/mL is available in 1 mL single dose vials and 5 mL multiple dose vials.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

BEFORE Haloperidol Decanoate Injection is administered, tell your health care provider if :

- You have heart disease, glaucoma or prostatic hypertrophy
- You are addicted to alcohol. You should not take Haloperidol Decanoate Injection if you are under the effects of alcohol.
- You are pregnant. Haloperidol Decanoate Injection should not be used during pregnancy unless your doctor considers the benefits to you markedly outweigh the potential risks to the fetus
- You are taking barbiturates, painkillers , narcotics or, antihistamines or other drugs that make you drowsy.
- You have any allergies to this drug or its ingredients
- You have or ever had a blackout or seizure
- You are breast feeding.

Haloperidol Decanoate Injection may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. You should be cautious when performing potentially hazardous tasks.

Effects on Newborns:
In some cases, babies born to a mother who used haloperidol decanoate during pregnancy have experienced symptoms that are severe and require the newborn 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.

People who use Haloperidol Decanoate Injection are cautioned:

- Against exposure to extreme heat
- That drugs such as Haloperidol Decanoate Injection increase the toxicity of certain types of insecticides ("organophosphorous" insecticides) including insecticides for agriculture (farming), treating animals (flea and tick control) and for treating pests around the house and garden. Be cautious if you must use these

products while using Haloperidol Decanoate Injection.

INTERACTIONS WITH THIS MEDICATION

Haloperidol Decanoate Injection can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on Haloperidol Decanoate Injection therapy.

Tell your doctor about all your prescription and over-the-counter medications, vitamins, minerals, herbal products (such as St. John's Wort), and drugs prescribed by other doctors. Do not start a new medication without telling your doctor.

Before using Haloperidol Decanoate Injection, tell your doctor if you regularly use other medicines that make you sleepy (such as cold or allergy medicine, narcotic pain medicine, sleeping pills, muscle relaxants, and medicine for seizures, depression, or anxiety). You should not use Haloperidol Decanoate Injection if you have drowsiness caused by other medications.

Drugs that may interact with Haloperidol Decanoate Injection include:
anti-anxiety agents, antidepressants, muscle relaxants, anti-seizure medicine, high blood pressure medicine, cabergoline, metrizamide, guanethidine, guanadrel, grepafloxacin, sparfloxacin, lithium, cisapride, atropine-like drugs, narcotic pain relievers (e.g., codeine), drugs used to aid sleep, drowsiness-causing antihistamines (e.g., diphenhydramine), other drugs that may make you drowsy.

Many cough-and-cold products contain ingredients that may add a drowsiness effect. Before using cough-and-cold medications, ask your doctor or pharmacist about the safe use of those products. Do not start or stop any medicine without doctor or pharmacist approval.

This list is not complete and there may be other drugs that can interact with Haloperidol Decanoate Injection.

PROPER USE OF THIS MEDICATION

This medication should be administered by deep intramuscular injection, preferably in the gluteus maximus, as prescribed. During the first few days your doctor may gradually increase your dose to allow your body to adjust to the medication. Do not increase the dosage or injection frequency without consulting your doctor. *Your condition will not improve any faster but the risk of serious side effects will be increased. Do not stop using this drug suddenly without your doctor's approval.*

Your doctor will decide which dose is best for you.

Usual dose:

The dose depends on your symptoms, and will be adjusted by your doctor to best treat those symptoms. The medication is delivered by injection in a large muscle, usually the buttocks.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdose symptoms may include agitation, and confusion, drowsiness, dizziness, muscle stiffness or twitching, increased salivation, trouble swallowing, weakness, loss of balance or coordination, and fainting.

Missed Dose:

Get the injection of the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to get the injection of the medicine and skip the missed dose. Do not double your dose to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, Haloperidol Decanoate Injection may cause some side effects. These side effects may be minor and temporary. However, some may be serious and need medical attention.

Side effects may include: sweating, urinary incontinence, dizziness, drowsiness, dry mouth, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes and blurred vision.

If any of these affects you severely, tell your doctor.

Your doctor should check your body weight before starting Haloperidol Decanoate Injection and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting Haloperidol Decanoate Injection. They will monitor 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 being treated.

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.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
	Neuroleptic Malignant Syndrome: any group of symptoms which may include high fever, sweating, stiff muscles, fast heartbeat, fast breathing and feeling confused, drowsy or agitated			✓
	Extrapyramidal Symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓
	Fast or irregular heartbeat		✓	
	Seizures or fits			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of penis			✓
	Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body		✓	
	Low Blood Pressure: feeling of Lightheadedness or fainting especially when getting up from a lying or sitting position		✓	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
	Decreased sweating		✓	
	Jaundice: yellow colour to skin and eyes, dark urine		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
	Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
	New or worsening constipation		✓	
	Akathisia: a feeling of restlessness, inability to remain motionless		✓	
	Vision Changes: blurred vision, glaucoma or other eye disorder		✓	
	Increased Blood Sugar: frequent urination, thirst and hunger	✓		

This is not a complete list of side effects. For any unexpected effects while usingHaloperidol Decanoate Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature 15-30ºC (59-86ºF). Do not refrigerate or freeze. Protect from light. Discard 28 days after initial puncture. Keep in carton until discarded.

Keep this and all medications out of the reach and sight of children.

IMPORTANT: PLEASE READ

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 www.healthcanada.gc.ca/medeffect
- 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 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

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 can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC
Etobicoke, Ontario M8Z 2S6

Prepared on: July 16, 2014

Mylan Pharmaceuticals ULC
Etobicoke, ON M8Z 2S6
1-800-575-1379
www.mylan.ca