PRODUCT MONOGRAPH

[Pr]HALOPERIDOL INJECTION

(Haloperidol)

5 mg/mL, 1 mL vial

Omega Standard

For intramuscular injection only. NOT FOR intravenous use.

Antipsychotic Agent

Omega Laboratories, Ltd.
11 177 Hamon
Montreal, QC, Canada
H3M 3E4

Date of Preparation:
March 21, 2011

Submission Control # 135063

Haloperidol Injection
5 mg/mL, 1 mL vial

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTION AND CLINICAL PHARMACOLOGY

Haloperidol Injection (intramuscular) is a butyrophenone derivative with antipsychotic properties that has been considered particularly effective in the management of hyperactivity, agitation and mania. Haloperidol is an effective neuroleptic and also 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 has not been clearly established, but it has been shown to be a dopamine receptor antagonist.

Peak plasma levels of haloperidol occur within about twenty minutes after intramuscular administration. Protein binding is 90% or more. Haloperidol is extensively metabolized by the liver and the metabolites are subsequently excreted in the urine and feces, *via* the bile. The half-life of elimination is 21 hours (range 13 to 35 hours).

INDICATIONS AND CLINICAL USE

Haloperidol Injection (intramuscular) is indicated for the rapid control of the acute manifestations of schizophrenia and manic states. It may also be of value in the management of aggressive and agitated behaviour in patients with chronic brain syndrome and mental retardation and in the symptomatic control of Gilles de la Tourette's syndrome.

CONTRAINDICATIONS

- Haloperidol Injection (intramuscular) is not to be used intravenously.
- Haloperidol Injection (intramuscular) 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, spastic diseases 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 preexisting Parkinson-like symptoms.
- **Use in Pregnancy and Lactation:** Safety of use of Haloperidol Injection (intramuscular) in pregnancy and lactation has not been established. 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.
- **Use in Children:** Safety and effectiveness in young children have not been established; therefore, Haloperidol Injection (intramuscular) is contraindicated in this age group.

WARNINGS

Cardiovascular Effects

CASES OF SUDDEN DEATH, QT PROLONGATION, AND TORSADE DE POINTES HAVE BEEN REPORTED IN PATIENTS RECEIVING HALOPERIDOL. HIGHER THAN RECOMMENDED DOSES OF ANY FORMULATION AND INTRAVENOUS ADMINISTRATION OF HALOPERIDOL APPEAR TO BE ASSOCIATED WITH A HIGHER RISK OF QT-PROLONGATION AND TORSADE DE POINTES. ALTHOUGH CASES HAVE BEEN REPORTED EVEN IN THE ABSENCE OF PREDISPOSING FACTORS, PARTICULAR CAUTION IS ADVISED IN TREATING PATIENTS WITH OTHER QT-PROLONGING CONDITIONS (INCLUDING ELECTROLYTE IMBALANCE [PARTICULARLY HYPOKALEMIA AND HYPOMAGNESEMIA], DRUGS KNOWN TO PROLONG QT, UNDERLYING CARDIAC ABNORMALITIES, HYPOTHYROIDISM, AND FAMILIAR LONG QT SYNDROME). **HALOPERIDOL MUST NOT BE ADMINISTERED INTRAVENOUSLY**. IF HALOPERIDOL IS ADMINISTERED INTRAVENOUSLY, THE ECG SHOULD BE MONITORED FOR QT PROLONGATION AND ARRHYTHMIAS.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although, the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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 relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs and 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 in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to **ADVERSE REACTIONS**).

Withdrawal Emergent Syndrome

Generally, patients receiving short-term antipsychotic therapy, experience no untoward effects if treatment is abruptly discontinued. However, in some patients, abrupt withdrawal of antipsychotic medication can precipitate transient dyskinetic signs which in certain cases are indistinguishable from tardive dyskinesia except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the incidence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw their use (see **ADVERSE REACTIONS**).

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with Haloperidol Injection (intramuscular).

Respiratory

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including Haloperidol Injection (intramuscular). It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Driving and Hazardous Activities

Haloperidol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

General

Although not reported with Haloperidol Injection (intramuscular), decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

PRECAUTIONS

Haloperidol Injection (intramuscular) should be administered cautiously to patients:

- With severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur. Instead, phenylephrine or norepinephrine should be used (see Cardiovascular Effects).

- Receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained (see Central Nervous System Effects).

- With known allergies, or with history of allergic reactions to drugs, including other neuroleptics.

- Receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione) (see Drug Interactions).

Central Nervous System Effects

Haloperidol may lower the convulsive threshold and has been reported to trigger seizures in previously controlled known epileptics. When instituting haloperidol therapy in these patients, adequate anticonvulsant medication should be maintained.

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

Although haloperidol is a relatively non-sedating 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 machinery.

Caution is also advised in patients with phaeochromocytoma and conditions predisposing to epilepsy, such as alcohol withdrawal and brain damage.

Psychiatric Effects

When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression.

Cardiovascular Effects

Administration to patients with severe cardiac disease should be guarded, despite the fact that haloperidol is well tolerated by patients with cardiac insufficiency. In very rare instances, it has been felt that haloperidol contributed to the precipitation of attacks in angina-prone patients. Moderate hypotension may occur with intramuscular administration or excessive oral doses of haloperidol; however, vertigo and syncope occur rarely. Haloperidol may antagonize the action of adrenaline and other sympathomimetic agents and reverse the blood pressure-lowering effects of adrenergic-blocking agents such as guanethidine.

General

Haloperidol has lowered the level of cholesterol in the serum and liver of monkeys. 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.

Skin and eye changes (ichthyosis and cataracts) have occurred with other butyrophenone derivatives but 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.

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 to intestinal obstructions.

Special Populations

Use in Pregnancy

There are no well-controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformation observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus.

Rodents given 2 to 20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced fertility, delayed delivery and pup mortality. No teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but cleft palate has been observed in mice given 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

Nursing Mothers

Infants should not be nursed during drug treatment.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of haloperidol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not consistently identified differences in responses between the elderly and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women (see **WARNINGS, Tardive Dyskinesia**). Also, the

pharmacokinetics of haloperidol in geriatric patients generally warrants the use of lower doses (see **DOSAGE AND ADMINISTRATION**).

Elderly or debilitated patients receiving the drug should be carefully observed for lethargy and a decreased sensation of thirst due to central inhibition which might lead to dehydration and reduced pulmonary ventilation.

Hepatic and Renal Impairment

As with other antipsychotic agents, haloperidol should be administered cautiously to patients with severe impairment of liver or kidney function.

Carcinogenicity, Mutagenicity and Impairment of Fertility

No mutagenic potential of haloperidol was found in the Ames Salmonella microsomal activation assay. Negative or inconsistent positive findings have been obtained in *in vitro* and *in vivo* studies of effects of haloperidol on chromosome structure and number. The available cytogenetic evidence is considered too inconsistent to be conclusive at this time.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumours. However, although a relatively greater number of rats survived to the end of the study in high-dose male and female groups, these animals did not have a greater incidence of tumours than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol-related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumour incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumours or specific tumour types were noted.

Antipsychotic 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, 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 antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumourigenesis: the available evidence is considered too limited to be conclusive at this time.

Drug Interactions

Lithium

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS, followed by irreversible brain damage) has occurred in a few patients treated with lithium plus haloperidol. A causal relationship has not been established; however, patients receiving such combined therapy should be monitored closely for evidence of neurological toxicity and treatment stopped immediately if such signs appear.

Antiparkinsonian Agents

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol is discontinued because of the difference in excretion rates. If both are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

CNS Depressants

Haloperidol Injection (intramuscular) may prolong the hypnotic action of barbiturates and may potentiate the effects of alcohol and other central nervous system depressant drug, such as

anesthetics and narcotics; caution should therefore be exercised when it is used with agents of this type and adjustments in dosage may be required.

Rifampin

In a study of 12 schizophrenic patients coadministered haloperidol and rifampin, plasma haloperidol levels were decreased by a mean of 70% and mean scores on the Brief Psychiatric Rating Scale were increased from baseline. In 5 other schizophrenic patients treated with haloperidol and rifampin, discontinuation of rifampin produced a mean 3.3-fold increase in haloperidol concentrations. Thus, careful monitoring of clinical status is warranted when rifampin is administered or discontinued in haloperidol-treated patients.

Methyldopa

Enhanced CNS defects have been reported when haloperidol is used in combination with methyldopa.

Anticoagulants

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

ADVERSE REACTIONS

Cardiovascular Effects

Tachycardia, hypotension and hypertension have been reported. QT prolongation and/or ventricular arrhythmias have also been reported, in addition to ECG pattern changes compatible with the polymorphous configuration of torsade de pointes, and may occur more frequently with high doses and in predisposed patients (see **WARNINGS** and **PRECAUTIONS**).

Central Nervous System Effects

Extrapyramidal Symptoms (EPS):

EPS during the administration of haloperidol have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs:

Generally, patients receiving short-term antipsychotic therapy, experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below 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 gradually withdraw use of haloperidol.

Tardive Dyskinesia:

As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson 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 reinstitue 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 tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia:

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:

Toxic confusional states, stupor, insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioural states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole

Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See **WARNINGS** for further information concerning NMS.)

Hematologic Effects

Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

Liver Effects

Impairment of liver function and/or jaundice or hepatitis has been reported rarely. One case of photosensitization is known and isolated cases of idiosyncratic cutaneous involvement have been observed.

Dermatologic Reactions

Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders

Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia.

Gastrointestinal Effects

Heartburn, anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting, weight loss, weight gain.

Autonomic Reactions

Dry mouth, blurred vision, urinary retention, diaphoresis and priapism and incontinence.

Respiratory Effects

Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses

Cataracts, retinopathy and visual disturbances.

Postmarketing Events

Hyperammonemia has been reported in a 5 ½ years old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

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 to 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 0701D
  Ottawa, ON 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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 reactions would be manifested by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively. With accidental overdosage, hypertension rather than hypotension occurred in a two year old child. The risk of ECG changes associated with torsade de pointes should be considered. (For further information regarding torsade de pointes, please refer to **WARNINGS** and **ADVERSE REACTIONS**.)

Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or in prolonged cases of

coma, by tracheotomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by the use of intravenous fluids, plasma or concentrated albumin, and vasopressor agents such as phenylephrine and norepinephrine. **Epinephrine should not be used**. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of QT prolongation of dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate antiarrhythmic measures.

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

DOSAGE AND ADMINISTRATION

DO NOT USE INTRAVENOUSLY.

As with all parenteral drug products, Haloperidol Injection (intramuscular) should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Do not use if precipitate appears and discard unused portion.

Adults

Haloperidol Injection (intramuscular) is administered for rapid control of acute psychotic symptoms. Dosages in the range of 2.5 to 5.0 mg are recommended and should be employed on a p.r.n. basis until the desired effect is achieved. Administration every 4 to 6 hours is sufficient in most cases although for resistant patients, the dosage may be repeated as often as every hour if required. Intramuscular administration of high doses may be accompanied by rapid appearance of extrapyramidal effects as control of symptomatology is achieved.

The oral form should supplant the injectable as soon as possible. For an initial approximation of the total daily dose required, the intramuscular dose administered in the preceding 24 hours may be used. Since this dose is only an initial estimate, it is recommended that careful monitoring of clinical signs and symptoms, including clinical efficacy, sedation and adverse effects be carried out periodically for the first several days following the switchover. In this way, dosage

adjustments, either upward or downward, can be quickly accomplished. Depending on the patient's clinical status, the first oral dose should be given within 12-24 hours following the last intramuscular dose.

Pediatrics

The safety and effectiveness of Haloperidol Injection (intramuscular) in children has not been established (see **CONTRAINDICATIONS**).

Geriatrics

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

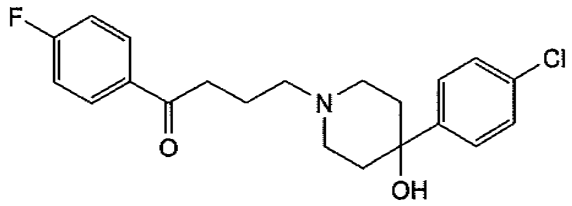
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: haloperidol

Chemical Name: 1-butanone, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1(4-fluorophenyl)

Structural Formula:



Molecular Formula: $C_{21}H_{23}ClFNO_2$

Molecular Weight: 375.87

Description: White or almost white amorphous or crystalline powder. Practically insoluble in water, very slightly soluble in ethanol, slightly soluble in ether, methylene chloride and methanol, soluble in chloroform.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C and 30°C. Protect from light.

Incompatibilities: DO NOT DILUTE WITH STERILE SALINE.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 1 mL amber vial contains: haloperidol 5 mg, lactic acid sufficient to adjust the pH within the range of 3.0 to 3.8 and water for injection USP.

Amber vials of 1 mL packaged in boxes of 10 x 1 mL.

PHARMACOLOGY

Haloperidol exerts pharmacological effects, characteristic of neuroleptic agents; it reduces locomotor and exploratory behaviour (ambulation and "emotional" defecation) in laboratory animals and at higher doses induces cataleptic immobility and ptosis, it suppresses the conditioned avoidance response in the jumping box test and blocks amphetamine-induced hyperactivity, and stereotypy, it suppresses apomorphine-induced emesis in dogs, it depresses food consumption and reduces weight gain, it abolishes the righting reflex in mice and prolongs barbiturate sleeping time. Haloperidol has relatively weak adrenolytic properties and at pharmacologically active doses it produces slight hypotension in the cat and hypothermia in the rat. In dogs and cats, the drug decreases the epinephrine-induced contractions of the nictitating membrane but is less effective against norepinephrine. Changes in the EEG activity produced by haloperidol are similar to those seen with phenothiazine derivatives.

Haloperidol blocks competitively postsynaptic dopamine receptors in the mesolimbic, nigrostriatal and tuberoinfundibular dopaminergic systems. Blockade of dopamine receptors in these areas is believed to bring about the antipsychotic, extrapyramidal and neuroendocrine actions of antipsychotic drugs, respectively.

TOXICOLOGY

Acute Toxicity

SPECIES	LD_{50} (mg/kg)		
	IV	SC	ORAL
Mice	13	54	144
Rats	22	63	850
Hamsters	-	-	405
Rabbits	8	-	-
Dogs	18	>80	90

Long-Term Toxicity

Species	Route of administration	Dose mg/kg/day	Duration	Results
Rat	Oral	1 3 10	12 months	No drug-induced abnormalities.
		3.5 6.5 14.5 33.0	18 months	No drug-induced abnormalities in blood, urine, laboratory parameters, gross pathology, histopathology. Body weights ↓, food consumption ↓, when compared to controls.
Dog	Oral	0.5 2.0	6 months	No drug-induced abnormalities.
		2.0 6.0 12.0	12 months	No deaths, decreased weight gain; convulsions, tremors and emesis at high doses; transient breast engorgement and lactation between 3rd and 8th weeks were not dose related; dose-related hepatocellular changes and elevated SGPT levels were reversible upon discontinuation of treatment.
Rat	Intramuscular	1.0 4.0	4 weeks	No abnormalities in hematology, organ weights or gross pathology. Inflammatory changes at the site of injection due to repeated injections.
Dog	Intramuscular	1.0 4.0	4 weeks	No abnormalities in hematology, organ weights or gross pathology. Inflammatory changes at the site of injection due to repeated injections.

Reproductive Studies

Study	Species	Route of administration	Dose mg/kg/day	Results
Pregnancy	Rat	Oral	0.073 0.65 1.90	Drug administered in the diet. Mating depressed in high-dose rats. No abnormalities occurred in 939 offspring. No significant difference between litter size of control and experimental groups. Offsprings from haloperidol-treated dams slightly smaller.
	Rat	Intravenous	0.6 1.8 3.0	Administered from 6th to 18th day post mating. No abnormalities observed in 663 offspring. No significant difference in litter size, mortality of the offspring or average delivery time.
	Dog	Oral	1.0 2.0 4.0	No malformations in 94 pups. No effect on pregnancy or average litter size.
Delivery	Rat	Intramuscular	0.125 0.25 1.0 4.0	Drug administered just prior to delivery. No abnormalities and no effect on litter size. Up to 1 mg/kg no effect on delivery time. At 4 mg/kg, increase in delivery time and increase in mortality of the young due to failure to remove placenta from the offspring by the depressed dams.
Lactation	Rat	Intravenous	0.6 1.8	From 1st to 6th day after delivery. Little or no significant difference in the mortality weight and gross pathology between the offspring from untreated control dams and those to which haloperidol was administered.

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PRECLINICAL

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