PRODUCT MONOGRAPH

Haloperidol Decanoate Injection

50 mg/mL, 100 mg/mL

For intramuscular injection only. NOT FOR intravenous use

Antipsychotic Agent

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Control number 124727

PRODUCT MONOGRAPH

Haloperidol Decanoate Injection 50 mg/mL, 100 mg/mL

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTION AND CLINICAL PHARMACOLOGY

Haloperidol decanoate (intramuscular), an ester derivative of haloperidol, possesses the antipsychotic properties of haloperidol. When it is administered as an intramuscular depot in sesame oil, esterases present in blood and tissues hydrolyse 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 one injection every four 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.

The pharmacokinetics were studied in chronic psychotic patients receiving monthly injections for up to two 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 four-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 three to six months, after which a steady-state was reached at levels about two to three times higher than in the first month of treatment.

Depending on the dose (25 to 400 mg haloperidol), 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 (intramuscular) in a concentration equivalent to 50 mg haloperidol/mL and subsequently were given a concentration equivalent to 100 mg haloperidol/mL. No significant differences in plasma levels were observed.

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

- Haloperidol decanoate (intramuscular) is not to be used intravenously.

- 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.

- **Use in pregnancy and lactation:**
  Safety 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. Haloperidol is excreted in breast milk.

- **Use in children:**
  Safety and efficacy have not been established; therefore, haloperidol decanoate 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 DECANOATE MUST NOT BE ADMINISTERED INTRAVENOUSLY.**

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 manifestation 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 treatment are available. There is no general agreement about specific pharmacological treatments 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 wth haloperidol.

Respiratory
A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. 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 decanoate (intramuscular) 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, 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 decanoate 50 (intramuscular) and haloperidol decanoate 100 (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 haloperidol has been reported to trigger seizures in previously controlled known epileptics. If indicated, adequate anticonvulsant therapy should be concomitantly maintained (see Central Nervous System Effects).
- with known allergies, or with a 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
Haloperidol may lower the convulsion threshold and has been reported to trigger seizures in previously controlled known epileptics. When instituting haloperidol therapy in these patients, adequate anti-convulsant therapy should be concomitantly maintained.

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

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 dangerous machinery.

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

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

Cardiovascular Effects
Administration to patients with severe cardiac involvement 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 was contributory 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 only 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 humans, 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 clinically with another butyrophenone derivative 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 may obscure signs of toxicity due to overdosage of other drugs or mask the symptoms of some organic diseases, such as brain tumour or intestinal obstructions.

Special Population

Usage in Pregnancy
There are no well-controlled studies 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, haloperidol decanoate (intramuscular) 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 up to 3 times the usual maximum human dose of haloperidol decanoate showed an increase in incidence of resorption, fetal mortality, and pup mortality. No fetal abnormalities were observed. Cleft palate has been observed in mice given oral haloperidol at 15 times the usual maximum 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
Since haloperidol is excreted in human breast mild, infants should not be nursed during drug treatment with haloperidol decanoate (intramuscular).

Pediatric Use
Safety and effectiveness of haloperidol decanoate (intramuscular) in children 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 **WARNING, Tardive Dyskinesia**). Also, the pharmacokinetics of haloperidol in geriatric patient 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No mutagenic potential of haloperidol decanoate 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 short-acting 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 between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Antiparkinsonian Agents

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol decanoate 50 (intramuscular) or haloperidol 100 decanoate (intramuscular) is

discontinued because of the prolonged action of haloperidol decanoate (intramuscular). 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 decanoate (intramuscular).

CNS Depressants
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.

Rifampin
In a study of 12 schizophrenic patients coadministered oral 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 effects may occur 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 this product is used together with anticoagulants.

ADVERSE REACTIONS

Adverse reactions following the administration of haloperidol decanoate 50 (intramuscular) or haloperidol 100 decanoate (intramuscular) are those of haloperidol. Since vast experience has accumulated with haloperidol, the adverse reactions are reported for that compound as well as for haloperidol decanoate (intramuscular). As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate (intramuscular).

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 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. Although the long-acting properties of haloperidol decanoate (intramuscular) provide gradual withdrawal, it is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs.

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 with haloperidol decanoate (intramuscular) 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 reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of 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, insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, stupor, 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 have 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, weight loss, weight gain, anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions
Dry mouth, blurred vision, urinary retention, incontinence diaphoresis, 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 5½ years old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In general, 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. With accidental overdosage, hypertension rather than hypotension occurred in a two year old child. The risk of ECG changes associated with torsades de pointe should be considered. (For further information regarding torsade de pointes, please refer to **WARNINGS** and **ADVERSE REACTIONS.**).

There is no specific antidote. Treatment is primarily supportive. A patient 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 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 or dysrhythmias and monitoring should continue until ECG is normal. Severe arrhythmias should be treated with appropriate antiarrhythmic measures.

DOSAGE AND ADMINISTRATION

DO NOT USE INTRAVENOUSLY.

As with all parenteral drug products, haloperidol decanoate (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, that does not clear upon warming to room temperature (see STABILITY AND STORAGE RECOMMENDATIONS), discolouration or leakage should not be used. Do not use if precipitate appears and discard unused portion.

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.

Adults
Administer by deep intramuscular injection, preferably in the gluteus maximus.

As a long-acting depot neuroleptic, haloperidol decanoate (intramuscular) has been found useful in the maintenance management of chronic schizophrenic patients. These patients have been stabilized with other medications, and might benefit from a transfer to longer acting injectable therapy. The changeover to haloperidol decanoate (intramuscular) 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 (intramuscular). 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 (intramuscular) should be based on the patient's symptomatology and previous oral neuroleptic dosage. A ratio of 20:1 of haloperidol decanoate (intramuscular) 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 (intramuscular) at lower doses and adjust the dose upwards as needed. There is limited experience with patients transferred to haloperidol decanoate (intramuscular) 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 (intramuscular) is four 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 four 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 three or even two weeks.

Clinical experience with haloperidol decanoate (intramuscular) at doses greater than 300 mg has been limited and much tower 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.

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

Pediatrics
The safety and efficacy of haloperidol 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

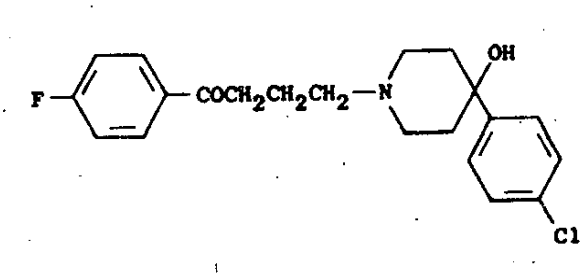
Drug substance:

Proper Name: haloperidol decanoate

Chemical Names: (1) Decanoic acid, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone

(2) Decanoic acid, ester with 4-[4-(p-chlorophenyl)-4-hydroxypiperidino1]-4'- fl uo robutyrophenone

Structural Formula:



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

Molecular Weight: 530.12

Description: Haloperidol decanoate is a white to pale yellow crystalline powder which melts at about 42°C. Haloperidol decanoate is freely soluble in alcohol, acetone and ether and slightly soluble in water.

STABILITY AND STORAGE RECOMMENDATIONS

Haloperidol Decanoate Injection should be stored between 15°C and 25°C, protected from light. As with other depot neuroleptics, precipitation may occur if the drug is stored for long periods in the cold. The precipitate should clear on storage at room temperature.

Warning: All parenteral drug products should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. The normal colour of Haloperidol Decanoate Injection is slightly amber. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

DOSAGE FORMS COMPOSITION AND PACKAGING

Haloperidol Decanoate Injection is available as either 50 mg/mL haloperidol (as the base)

in 5 mL vials or as 100 mg/mL haloperidol (as the base), in 1 mL ampoules or 5 mL vials.

Composition:
(1) 50 mg/mL vials. Each mL of slightly amber, viscous solution contains 50 mg of haloperidol (as 70.5 mg of haloperidol decanoate) in sesame oil, with 12 mg of benzyl alcohol as preservative.

(2) 100 mg/mL ampoules. Each mL of slightly amber, viscous solution contains 100 mg of haloperidol (as 141 mg of haloperidol decanoate) in sesame oil, with 15 mg of benzyl alcohol as preservative.

(3) 100 mg/mL vials. Each mL of slightly amber, viscous solution contains 100 mg of haloperidol (as 141 mg of haloperidol decanoate) in sesame oil, with 12 mg of benzyl alcohol as preservative.

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 prolonged 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 liver and adrenals. Markedly lower levels were found in the brain, lung, kidney, fat and skeletal muscle. Tissue concentrations exceed 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 prodrug 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 50 mg eq/mL formulation and 800 mg/kg using the 100 mg eq/mL formulation.

Similar side effects were observed in rats dosed with either of the two drug formulations. These include decreased activity, relaxed palpebræ, unkempt appearance, chromorhinorrhea and hyperactivity to touch. Chromodacryorrhea, hyperemia of the skin and paw pads, hunched posture, thin appearance, urine stained abnormal 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 IM, 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 incident 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 IM 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 study, 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 occurred 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 IV 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 parenchyma 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 parenchyma pigmentation at 5.0 and 1.25 mg/kg, and an increase in spleen follicular pigmentation, mammary gland development and parenchyma 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 g/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 anæmia 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 1.25 and 5.0 mg/kg.

Other histopathological changes occurring at increased incidence in treated mice were 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.

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29. Product Monograph, Haloperidol LA (Haloperidol Decanoate Injection) 50 mg haloperidol/mL, 100 mg haloperidol/mL. Sandoz Canada Inc. Revised January 10, 2008, Control No. 117509.