

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 15-923/S-072

Name: Haldol Injection (IR)

Generic Name: haloperidol lactate

Sponsor: Ortho-McNeil Pharmaceutical, Inc.

Approval Date: 04/17/2002

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APPLICATION NUMBER:
NDA 15-923/S-072

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APPROVAL LETTER



NDA 15-921 / S-076
NDA 15-922 / S-066
NDA 15-923 / S-072
NDA 18-701 / S-046

The R.W. Johnson Pharmaceutical Research Institute
Attention: Susie Merchant
920 Route 202
POB 300
Raritan, NJ 08869-0602

Dear Ms. Merchant:

Please refer to your supplemental new drug applications dated December 6, 2001, received December 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Haldol (haloperidol) Tablets, Concentrate, Injection, and Haldol (haloperidol) Decanoate Injection

These "Changes Being Effected" supplemental new drug applications provide for labeling changes as requested in our letter of September 25, 2000, specifically modification of labeling text to more clearly state that these agents are indicated for the treatment of schizophrenia.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted December 6, 2001). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz

4/17/02 08:23:15 AM

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APPLICATION NUMBER:

NDA 15-923/S-072

REPRESENTATIVE LABELING

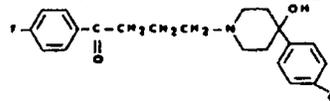
Revised September 2001
643-94-067-6



HALDOL®
brand of
haloperidol
Injection
(For Immediate Release)

DESCRIPTION

Haloperidol is the first of the butyrophenone series of major antipsychotics. The chemical designation is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-1-piperazinebutyrophenone and it has the following structural formula:



HALDOL (haloperidol) is available as a sterile parenteral form for intramuscular injection. The injection provides 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per mL, and lactic acid for pH adjustment between 3.0 - 3.6.

ACTIONS

The precise mechanism of action has not been clearly established.

INDICATIONS

HALDOL (haloperidol) is indicated for use in the treatment of schizophrenia.

HALDOL is indicated for the control of tics and vocal utterances of Tourette's Disorder.

CONTRAINDICATIONS

HALDOL (haloperidol) is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

WARNINGS

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 tardive dyskinesia 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, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear 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.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (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 HALDOL.

Usage in Pregnancy—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.

There are no well controlled studies with HALDOL (haloperidol) in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of HALDOL 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 HALDOL, 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. Infants should not be nursed during drug treatment.

Combined Use of HALDOL and 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 HALDOL. A causal relationship between these events and the concomitant administration of lithium and HALDOL 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.

General—A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including HALDOL. 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.

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

HALDOL 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.

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

PRECAUTIONS

HALDOL (haloperidol) 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 HALDOL may block its vasoconstrictor activity and paradoxically further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.

- receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.

- with known allergies, or with a history of allergic reactions to drugs.

- receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after HALDOL 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 HALDOL.

As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

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.

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

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

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 3 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 tumors. 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 tumors 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 tumor 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 tumors or specific tumor 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 tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

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).

ADVERSE REACTIONS

CNS Effects:

Extrapyramidal Symptoms (EPS)—EPS during the administration of HALDOL (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 dyskinesic signs after abrupt withdrawal. In certain of these cases the dyskinesic 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 HALDOL.

Tardive Dyskinesia.—As with all antipsychotic agents HALDOL 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 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, this syndrome may be masked.

It has been reported that fine vermicular movement 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.—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral 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 HALDOL. (See WARNINGS for further information concerning NMS.)

Cardiovascular Effects.—Tachycardia, hypotension, hypertension and ECG changes including prolongation of the Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsade de pointes.

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 HALDOL, and then only in association with other medication.

Liver Effects.—Impaired liver function and/or jaundice have been reported.

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 hypotatemia.

Gastrointestinal Effects.—Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions.—Dry mouth, blurred vision, urinary retention, diaphoresis and priapism.

Respiratory Effects.—Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses.—Cataracts, retinopathy and visual disturbances.

Other.—Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL 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 antipsychotic drugs.

Postmarketing Events.—Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with HALDOL.

OVERDOSAGE

Manifestations.—In general, the symptoms of overdose would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) 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 agitated types respectively. With accidental overdose, hypotension 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 ADVERSE REACTIONS.)

Treatment.—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 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 metaraminol, 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 Q-T prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

DOSAGE AND ADMINISTRATION

There is considerable variation from patient to patient in the amount of medication required for treatment. As with all drugs used to treat schizophrenia, dosage should be individualized according to the needs and response of each patient. Dosage adjustments, either upward or downward, should be carried out as rapidly as practicable to achieve optimum therapeutic control.

To determine the initial dosage, consideration should be given to the patient's age, severity of illness, previous response to other antipsychotic drugs, and any concomitant medication or disease state. Debilitated or geriatric patients, as well as those with a history of adverse reactions to antipsychotic drugs, may require less HALDOL (haloperidol). The optimal response in such patients is usually obtained with more gradual dosage adjustments and/or lower dosage levels.

Parenteral medication, administered intramuscularly in doses of 2 to 5 mg, is utilized for prompt control of the acutely agitated schizophrenic patient with moderately severe to very severe symptoms. Depending on the response of the patient, subsequent doses may be given, administered as often as every hour, although 4 to 8 hour intervals may be satisfactory.

Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Switchover Procedure

An oral form should supplant the injectable as soon as practicable. In the absence of bioavailability studies establishing bioequivalence between these two dosage forms the following guidelines for dosage are suggested. For an initial approximation of the oral daily dose required, the parenteral 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 initiation of 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 parenteral dose.

HOW SUPPLIED

HALDOL[®] brand of haloperidol Injection (For Immediate Release) 5 mg per mL (as the lactate) — NDC 0045-0255-01, units of 10 x 1 mL ampuls and NDC 0045-0255-49, 10 mL multiple-dose vial.

Store HALDOL[®] haloperidol Injection at controlled room temperature (15°-30°C, 59°-86°F). Protect from light. Do not freeze.

ORTHO-MCNEIL

OMP DIVISION
ORTHO-MCNEIL
PHARMACEUTICAL, INC.
Raritan, New Jersey 08869

Printed in U.S.A.

Revised September 2001
613 94-067 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 15-923/S-072

MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data
NDA #15-923**

Sponsor: R. W. Johnson
Drug: Haldol Injection (IR)
Approved Indication: Schizophrenia
Material Submitted: SLR-072: Response to Request for Labeling Change
Correspondence Date: December 6, 2001
Date Received: December 10, 2001

On 9-25-00, the Division issued a letter to all holders of NDA's for antipsychotic drug products that requested modification of labeling text to more clearly indicate that these agents are indicated for the treatment of schizophrenia. This submission contains the response from R.W. Johnson Pharmaceutical Research Institute with respect to Haldol (haloperidol) Injection (immediate-release).

Additionally, this supplement adds a Pediatric Use subsection to PRECAUTIONS to state that safety and effectiveness in pediatric patients have not been established.

Final Printed Labeling was reviewed and changes pursuant to our 9-25-00 request are acceptable. The statement regarding use in pediatric patients is also acceptable. These changes were effective 11-30-01.

It is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.
January 14, 2002

cc: NDA #15-923
HFD-120 (Division Files)
HFD-120/GDubitsky
/TLaughren
/SHardeman

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/s/

Greg Dubitsky
1/14/02 11:15:34 AM
MEDICAL OFFICER

Thomas Laughren
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MEDICAL OFFICER