CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 18-701/S-046

Name: Haldol Injection (IM)

Generic Name: haloperidol decanoate

Sponsor: Ortho-McNeil Pharmaceutical, Inc.

Approval Date: 04/17/2002
APPLICATION NUMBER:
NDA 18-701/S-046

CONTENTS

Reviews / Information Included in this Review

<table>
<thead>
<tr>
<th>Review Type</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Approvable Letter(s)</td>
<td></td>
</tr>
<tr>
<td>Representative Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
</tr>
<tr>
<td>EA/FONSI</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative and Correspondence Document(s)</td>
<td></td>
</tr>
</tbody>
</table>
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 18-701/S-046

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 Effectuated" 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.
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
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 18-701/S-046

REPRESENTATIVE LABELING
Haldol Decanoate 50 (haloperidol) and Haldol Decanoate 100 (haloperidol) are long-acting forms of Haldol (haloperidol). The basic effects of haloperidol are the same as those of Haldol, but the duration of action is longer. Haldol Decanoate 50 is for IM injection only. Haldol Decanoate 100 is for IM injection only.

INDICATIONS AND USAGE
Haldol Decanoate 50 and Haldol Decanoate 100 are indicated for the treatment of schizophrenia patients who require prolonged parenteral antipsychotic therapy. Contraindications

Contraindications, Warnings, and additional information are those of Haldol, modified only to reflect the differences in dosage and duration of action.

Haldol is contraindicated in severe toxic central nervous system depression or coma states from any cause and in individuals who have shown a previous allergic reaction to this drug or who have Parkinson’s disease.

WARNINGS Tardive Dyskinesia—A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements which may occur at any point during the course of therapy, especially during an older age population. It characteristically involves the tongue, the face, and the orofacial region. It may also involve the extremities and the body. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with the duration of therapy and the total cumulative dose of antipsychotic drug administered to the patient. However, the syndrome can develop, although much less commonly, after relatively brief periods of low doses. There is no known treatment for established cases of tardive dyskinesia, although the symptoms may remit, partially or completely, if antipsychotic drug therapy is withdrawn. However, the likelihood of remission is less if the drug is withdrawn from patients receiving high weekly dosages of antipsychotic drug for a prolonged period of time. In patients who have developed symptoms of tardive dyskinesia, the drug should be cautiously tapered off and monitored closely.

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 not require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The use of combination therapy should be avoided.

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.

The diagnostic evaluation of patients with this syndrome is complicated. At arrival in a diagnostic situation, it is necessary to identify cases where the clinical presentation includes other serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated depression or other psychiatric disorders (e.g., schizophrenia, dysthymia, and depressive disorder).

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinically, NMS is characterized by hyperpyrexia, increased muscle tone and rigidity, altered mental status (including catatonic-like) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia or bradycardia, hyperpyrexia, hypotension, etc.). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

Given the clinical appearance of this syndrome is complicated, at arrival in a diagnostic situation, it is necessary to identify cases where the clinical presentation includes other serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated depression or other psychiatric disorders (e.g., schizophrenia, dysthymia, and depressive disorder).

The management of NMS should include 1) immediate discontinue of antipsychotic drugs and other drugs not essential to concur treatment, 2) intensive symptomatic and supportive treatment, and 3) treatment of the underlying serious medical problems for which specific treatments are indicated. There is no agreed upon strategy about specific neuroleptic treatment regimens for patients with NMS.
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 a predictable human risk for most of these drugs. However, there are uncounted and well-controlled studies in pregnant women. These reports, however, are often in patients with diabetes mellitus, and others have reported an increased risk of maternal hypertension in there are some agents that have been associated with hypertension. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to the use of the drug, patients should be used during pregnancy or in women likely to become pregnant only if the benefit certainly justifies a potential risk to the fetus.

Nursing Mothers

No adverse effects in human breast milk, infants should not be nursed during drug treatment with haloperidol decanoate.

Pediatric Use

Safety and effectiveness of haloperidol decanoate in children have not been established.

Geriatric Use

Clinical experience with haloperidol decanoate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Older reports 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 and ADVERSE REACTIONS). Also, the pharmacokinetics of haloperidol in geriatric patients generally warrant the use of lower doses (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL (haloperidol). The adverse reactions associated with this compound as well as with haloperidol decanoate. As with all injectable medicaments, local tissue reactions have been reported with haloperidol decanoate.

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’s-like symptoms, akathisia, or dyskinesia (including echopraxia and acalculic apraxia). While all can occur as 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 antiparkinsonism drugs such as benzztropine 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.

Withdrawn Emergent Neurological Signs—Generally, patients receiving short-term therapy experience to problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dystonic signs after abrupt withdrawal. In certain of these cases the dystonic movements are indistinguishable from the syndrome described below under “Tardive Dyskinesia” except for duration. Although the long-acting properties of haloperidol decanoate 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 HALDOL has been associated with persistent tardive dyskinesia. Tardive dyskinesia, a syndrome of orofacial dyskinesia, an essentially irreversible, involuntary, dyskinetic movement, most often appears by a period of years, but may occur after relatively short periods in some patients. Tardive dyskinesia may be accompanied by involuntary movements of the trunk, limbs, face, or neck. There is no known effective treatment for tardive dyskinesia. In patients with tardive dyskinesia or a history of antipsychotic use, the clinician should be aware that tardive dyskinesia may be precipitated by the clinician.

Tardive Dyskinesia—Tardive dyskinesia, not associated with the above syndrome, has also been reported. Tardive dyskinesia is characterized by delayed onset of chorea or dystonic movements, is often permanent, and has the potential of being irreversible.

Other CNS Effects—In unusual instances, anxiety, agitation, confusion, depression, dizziness, drowsiness, hallucinations, hypomania, insomnia, irritability, masked facies, nervousness, unusual thoughts, and insomnia may be noted.

Body as a Whole—Neurologic/muscular syndromes (NSD), hypotension and hemorrhage have been reported with this drug. Haloperidol decanoate has been implicated in many instances of death due to antipsychotic drug intoxication.

Cardiovascular Effects—Tachycardia, hypotension, and hypertension and ECG changes including prolongation of the QT- interval and ECG pattern changes comparable to the polymorphic configurations of torsades de pointes. Hemorrhagic Effects—Reports have appeared relating the occurrence of mild and unusually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphocytosis. 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 acniform skin reactions and isolated cases of phototoxicity and loss of hair have been reported.

Endocardial Disease—Lacunar, breast enlargement, mastalgia, menstrual irregularity, myopathy, fatigue, increased libido, hyponatraemia, hypothyroidism, and hypoglycemia.

Gastrointestinal Effects—Anosmia, constipation, diarrhea, dysphagia, dyspepsia, nausea and vomiting.

Anticholinergic Effects—Dry mouth, blurred vision, urinary retention, and constipation.

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

Special Senses—Cataracts, retinopathy and visual disturbances.

Other Effects—Cases of sudden unexpected death has been associated 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 could death cannot, of course, be excluded, but it is not considered to be a causal factor in unexpected deaths which occur in psychiatric patients when they go untreated or when they are treated with other antipsychotic drugs.

Postmarketing Events: Hyperthermia has been reported in a 7-year old child with childhood-onset, an inherited disorder of ammonia excretion, following treatment with HALDOL.

OVERDOSAGE

While overdosage is less likely to occur with a potential than with an oral medication, information pertaining to HALDOL (haloperidol)

DOSE AND ADMINISTRATION

HALDOL Decanoate 50 and HALDOL Decanoate 100 should be administered by deep intramuscular injection. A 7.5 g needle gauge is recommended. The maximum volume per injection site should not exceed 3 ml. DO NOT ADMINISTER INTRAVENTRICULARLY. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and syringe are used.

HALDOL Decanoate 50 and HALDOL Decanoate 100 are intended for use in schizophrenic patients who require prolonged antipsychotic treatment. These patients should be previously stabilized on antipsychotic medication before considering a conversion to haloperidol decanoate. Furthermore, it is recommended that patients being considered for haloperidol decanoate therapy have been treated with and tolerate well, short-acting HALDOL (haloperidol) in order to reduce the possibility of an unexpected adverse reaction to haloperidol decanoate.

Close clinical supervision is required during the initial period of dose adjustment in order to minimize the risk of overdose or rekindling of previous psychotic symptoms before the next injection. During dose adjustment or episodes of exacerbation of symptoms of schizophrenia, haloperidol decanoate therapy can be supplemented with short-acting forms of haloperidol.

The dose of HALDOL Decanoate 50 or HALDOL Decanoate 100 should be expressed in terms of its haloperidol content. The starting dose of haloperidol decanoate should be based on the patient’s age, clinical history, physical condition, and response to previous antipsychotic therapy. The treatment approach to determine the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed. For patients previously maintained on low doses of antipsychotics (e.g., up to the equivalent of 2 mg per day chlorpromazine), it is recommended that the initial dose of haloperidol decanoate be 15-30 mg the previous daily dose in oral haloperidol equivalent. Patients with limited clinical experience suggests that lower initial doses may be adequate.

Initial Therapy

Conversion from oral haloperidol to haloperidol decanoate can be achieved by using an initial dose of haloperidol decanoate that is 10 to 15 mg more than the oral haloperidol dose that produced the desired clinical response.

In patients who are elderly, debilitated, or take low doses of oral haloperidol (e.g., up to the equivalent of 0.5 mg/day oral haloperidol), a range of 15-30 mg the previous oral haloperidol equivalent is appropriate for initial conversion.

In patients previously maintained on higher doses of antipsychotics (e.g., up to the equivalent of 5 mg per day chlorpromazine), it is recommended that the initial dose of haloperidol decanoate be 50-60 mg the previous daily dose in oral haloperidol equivalent. This approach was associated with clinical improvement and did not result in an increase in the duration of haloperidol decanoate therapy. Initial dose should be administered in two injections, i.e., a maximum of 100 mg initially followed by the balance in 3 to 7 days.

Maintenance Therapy

The maintenance dosage of haloperidol decanoate must be individualized with titration upward or downward based on therapeutic response. The usual maintenance range is 10 to 15 mg the previous daily dose in oral haloperidol equivalent. The clinical response of the patient.

HALDOL DECANOATE DOSING RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Patients</th>
<th>1st Month</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-15 mg Daily Oral Dose</td>
<td>10-15 mg Previous Daily Oral Dose</td>
</tr>
<tr>
<td>Morbidly Depressed</td>
<td>10-15 mg Daily Oral Dose</td>
<td>10-15 mg Previous Daily Oral Dose</td>
</tr>
<tr>
<td></td>
<td>20-30 mg Daily Oral Dose</td>
<td>20-30 mg Previous Daily Oral Dose</td>
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Relief of Tardive Dyskinesia

Clinical experience with haloperidol decanoate at doses greater than 540 mg per month has been limited.

HOW SUPPLIED

HALDOL (haloperidol) Decanoate 50 for IM injection, 50 mg haloperidol as 70.5 mg per ml haloperidol decanoate—NDC 0005-0233. 100 mg haloperidol as 141.0 mg per ml haloperidol decanoate—NDC 0005- 0250, 5 x 1 ml ampuls and 5 ml multiple dose vial.

HALDOL (haloperidol) Decanoate 100 for IM injection, 100 mg haloperidol as 141.04 mg per ml haloperidol decanoate—NDC 0005- 0255, 5 x 1 ml ampuls and 5 ml multiple dose vial.

Store at room temperature (15-30°C, 59-86°F). Do not refrigerate or freeze. Protect from light.

OMOP DIVISION
ORTHO-MUCOS
PHARMACEUTICALS, INC.
ORIZED, PA 19085

Revised September 2001
649-94-253-1
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 18-701/S-046

MEDICAL REVIEW(S)
Review and Evaluation of Clinical Data
NDA #18-701

Sponsor: R. W. Johnson
Drug: Haldol Decanoate Injection
Approved Indication: Schizophrenia
Material Submitted: SLR-046: 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) Decanoate Injection.

Final Printed Labeling was reviewed and changes pursuant to our 9-25-00 request are 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 #18-701
HFD-120 (Division Files)
HFD-120/GDubitsky
/TLaughren
/SHardeman
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Greg Dubitsky
1/14/02 01:12:55 PM
MEDICAL OFFICER

Thomas Laughren
1/14/02 02:57:14 PM
MEDICAL OFFICER