

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number : 074811**

**Trade Name : HALOPERIDOL DECANOATE  
INJECTION, 50MG (BASE) /ML**

**Generic Name: Haloperidol Decanoate Injection 50mg  
(base)/ml**

**Sponsor : Bedford Laboratories**

**Approval Date: January 30, 1998**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION**                      **074811**

**CONTENTS**

	<b>Included</b>	<b>Pending Completion</b>	<b>Not Prepared</b>	<b>Not Required</b>
<b>Approval Letter</b>	<b>X</b>			
<b>Tentative Approval Letter</b>				
<b>Approvable Letter</b>				
<b>Final Printed Labeling</b>	<b>X</b>			
<b>Medical Review(s)</b>				
<b>Chemistry Review(s)</b>	<b>X</b>			
<b>EA/FONSI</b>				
<b>Pharmacology Review(s)</b>				
<b>Statistical Review(s)</b>				
<b>Microbiology Review(s)</b>				
<b>Clinical Pharmacology Biopharmaceutics Review(s)</b>				
<b>Bioequivalence Review(s)</b>	<b>X</b>			
<b>Administrative Document(s)</b>				
<b>Correspondence</b>				

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number                      074811**

**APPROVAL LETTER**

ANDA 74-811

JAN 30 1998

Bedford Laboratories  
Attention: Shahid Ahmed  
300 Northfield Road  
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 21, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Haloperidol Decanoate Injection, 50 mg (base)/mL.

Reference is also made to your amendments dated May 14, November 21, and December 15, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Haloperidol Decanoate Injection, 50 mg (base)/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Haldol® Decanoate-50 Injection, 50 mg (base)/mL, of RW Johnson Pharmaceutical Research Institute).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours

A large black rectangular redaction covers the signature area. A small white box with the letters "IS" is visible within the redacted area.

Douglas L. Spork  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

*[Handwritten signature]*  
1-30-98

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      074811**

**FINAL PRINTED LABELING**

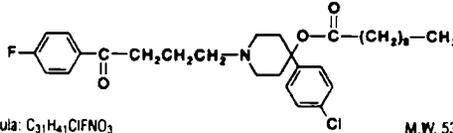


# HALOPERIDOL DECANOATE INJECTION

For IM Injection Only

## DESCRIPTION

Haloperidol decanoate is the decanoate ester of the butyrophenone, haloperidol. It has a markedly extended duration of effect. It is available in sesame oil in sterile form for intramuscular (IM) injection. The structural formula of haloperidol decanoate, 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone decanoate, is:



Molecular Formula:  $\text{C}_{31}\text{H}_{41}\text{ClFNO}_3$

M.W. 530.13

Haloperidol decanoate is almost insoluble in water (0.01 mg/mL), but is soluble in most organic solvents.

Each mL of Haloperidol Decanoate Injection, 50 mg/mL, contains 50 mg haloperidol (present as haloperidol decanoate 70.52 mg) in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

## CLINICAL PHARMACOLOGY

Haloperidol decanoate is the long-acting form of haloperidol. The basic effects of haloperidol decanoate are no different from those of haloperidol with the exception of duration of action. Haloperidol blocks the effects of dopamine and increases its turnover rate; however, the precise mechanism of action is unknown.

Administration of haloperidol decanoate in sesame oil results in slow and sustained release of haloperidol. The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about three weeks. Steady state plasma concentrations are achieved after the third or fourth dose. The relationship between dose of haloperidol decanoate and plasma haloperidol concentration is roughly linear for doses below 450 mg. It should be noted, however, that the pharmacokinetics of haloperidol decanoate following intramuscular injections can be quite variable between subjects.

## INDICATIONS AND USAGE

Haloperidol Decanoate Injection, is a long-acting parenteral antipsychotic drugs intended for use in the management of patients requiring prolonged parenteral antipsychotic therapy (e.g., patients with chronic schizophrenia).

## CONTRAINDICATIONS

Since the pharmacologic and clinical actions of Haloperidol Decanoate Injection, are attributed to haloperidol as the active medication, contraindications, warnings, and additional information are those of haloperidol, modified only to reflect the prolonged action.

Haloperidol is contraindicated in severe 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 haloperidol.

**General** - 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.

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

**PRECAUTIONS**

Haloperidol decanoate 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, metaraminol, phenylephrine or norepinephrine should be used.
- receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- 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 haloperidol decanoate is discontinued because of the prolonged action of haloperidol decanoate. If both drugs 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.

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

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

**Information for Patients**

Haloperidol decanoate 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.

**Drug Interactions**

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.

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

**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 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.

**Pregnancy: Teratogenic Effects: Pregnancy Category C.**

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 human dose. Cleft palate in mice appears to be a non-specific 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 adequate and well-controlled studies in pregnant women. There are reports, however, of cases of limb malformations 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 with these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, haloperidol decanoate should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus.

**Nursing Mothers**

Since haloperidol is excreted 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.

**ADVERSE REACTIONS**

Adverse reactions following the administration of Haloperidol Decanoate Injection, 50 mg/mL 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. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

**CNS 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 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 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 haloperidol. (See **WARNINGS** for further information concerning NMS.)

**Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes including prolongation of Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsades 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 haloperidol, 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 hyponatremia.

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

**Postmarketing Events:** Hyperammonemia has been reported in a 5 1/2 year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

**OVERDOSAGE**

While overdosage is less likely to occur with a parenteral than with an oral medication, information pertaining to haloperidol is presented, modified only to reflect the extended duration of action of haloperidol decanoate.

**Manifestations** - In general, the symptoms of overdosage 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 reactions would be manifested by muscular weakness or rigidity and a generalized or localized tremor, as demonstrated

4

by the akinetic or agitated 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 pointes should be considered. (For further information regarding torsades de pointes, please refer to **ADVERSE REACTIONS**.)

**Treatment** - Since there is no specific antidote, treatment is primarily supportive. 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, and should be continued for several weeks, and then withdrawn gradually as extrapyramidal symptoms may emerge.

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

Haloperidol Decanoate Injection, 50 mg/mL should be administered by deep intramuscular injection. A 21 gauge needle is recommended. The maximum volume per injection site should not exceed 3 mL. **DO NOT ADMINISTER INTRAVENOUSLY.**

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

Haloperidol Decanoate Injection, 50 mg/mL, is intended for use in chronic psychotic patients who require prolonged parenteral antipsychotic therapy. 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 haloperidol in order to reduce the possibility of an unexpected adverse sensitivity to haloperidol.

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

The dose of haloperidol decanoate 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 preferred approach to determining 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 10 mg/day oral haloperidol), it is recommended that the initial dose of haloperidol decanoate be 10 to 15 times the previous daily dose in oral haloperidol equivalents; 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 20 times the previous daily dose in oral haloperidol equivalents.

In patients who are elderly, debilitated, or stable on low doses of oral haloperidol (e.g., up to the equivalent of 10 mg/day oral haloperidol), a range of 10 to 15 times the previous daily dose in oral haloperidol equivalents is appropriate for initial conversion.

In patients previously maintained on higher doses of antipsychotics for whom a low dose approach risks recurrence of psychiatric decompensation and in patients whose long term use of haloperidol has resulted in a tolerance to the drug, 20 times the previous daily dose in oral haloperidol equivalents should be considered for initial conversion, with downward titration on succeeding injections.

The initial dose of haloperidol decanoate should not exceed 100 mg regardless of previous antipsychotic dose requirements. If, therefore, conversion requires more than 100 mg of haloperidol decanoate as an initial dose, that 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 times the previous daily dose in oral haloperidol equivalents dependent on the clinical response of the patient.

#### HALOPERIDOL DECANOATE DOSING RECOMMENDATIONS

PATIENTS	MONTHLY 1ST MONTH	MAINTENANCE
Stabilized on low daily oral doses (up to 10 mg/day)	10 - 15x Daily Oral Dose	10-15x Previous Daily Oral Dose
Elderly or Debilitated		
High dose	20x Daily Oral Dose	10-15x Previous Daily Oral Dose
Risk of relapse		
Tolerant to oral haloperidol		

Close clinical supervision is required during initiation and stabilization of haloperidol decanoate therapy.

Haloperidol decanoate is usually administered monthly or every 4 weeks. However, variation in patient response may dictate a need for adjustment of the dosing interval as well as the dose. (See **CLINICAL PHARMACOLOGY**.)

Clinical experience with haloperidol decanoate at doses greater than 450 mg per month has been limited.

#### HOW SUPPLIED

Haloperidol Decanoate Injection, 50 mg/mL for IM injection, 50 mg haloperidol as 70.5 mg per mL haloperidol decanoate -  
NDC 55390-412-01, 10 x 1 mL vials  
NDC 55390-412-05, 5 mL multiple dose vials

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

Manufactured For: Bedford Laboratories™  
Bedford, Ohio 44146

Manufactured By: Ben Venue Laboratories, Inc.  
Bedford, Ohio 44146

September, 1996

HALP00

Format # 186A

- 288 BLUE
- BLACK

30



1-3/8

**HALOPERIDOL**  
DECANOATE INJECTION



\*Each mL contains 50 mg haloperidol as 70.5 mg haloperidol decanoate in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

NDC 55390-412-05  
5 mL Multiple Dose Vial

USUAL DOSAGE: See package insert

NDC 55390-412-05  
5 mL Multiple Dose Vial

**HALOPERIDOL**  
DECANOATE INJECTION

Store at controlled room temperature 15° to 30°C (59° to 86°F)  
Do not refrigerate or freeze.

**HALOPERIDOL**  
DECANOATE INJECTION



Protect from light.



Keep in carton until empty.

FOR IM USE ONLY

Manufactured by:  
Ben Venue Labs, Inc  
Bedford, OH 44146

FOR IM USE ONLY

Manufactured for:  
Bedford Laboratories™  
Bedford, OH 44146

Sterile

Sterile



The dose of Haloperidol Decanoate should be expressed in terms of its haloperidol content.

CAUTION: Federal law prohibits dispensing without prescription.



1-3/8

LOT  
EXP

HALCC00

2-1/2

+

+

NDC 55380-412-01 5 mL Multiple Dose Vial

**HALOPERIDOL  
DECANOATE INJECTION**

USUAL DOSAGE: See package insert.

Each mL contains 50 mg haloperidol as 75.5 mg haloperidol decanoate in a benzene oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

The dose of Haloperidol Decanoate should be restricted in terms of its haloperidol content.

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

CAUTION: Federal law prohibits dispensing without prescription.

25 THRU 500 MG  
FOR IM USE ONLY  
Sterile

Mfg. by:  
Bart Vitrol Labs, Inc.  
Buffalo, OH 44146

Mfg. by:  
Bart Vitrol Laboratories™  
Buffalo, OH 44146

LOT  
EXP

NDC 55380-412-01 1 mL

**HALOPERIDOL  
DECANOATE INJECTION**

USUAL DOSAGE: See package insert.

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

CAUTION: Federal law prohibits dispensing without prescription.

25 THRU 500 MG  
FOR IM USE ONLY  
Sterile

Mfg. by:  
Bart Vitrol Labs, Inc.  
Buffalo, OH 44146

Mfg. by:  
Bart Vitrol Laboratories™  
Buffalo, OH 44146

**BEDEKORD**  
LABORATORIES<sup>SM</sup>

Sterile

FOR IM USE ONLY

50 mg/mL\*

**HALOPERIDOL DECANOATE INJECTION**

10 X 1 mL VIALS

NDC 55390-412-01



**USUAL DOSAGE:** See package insert.  
\*Each mL contains 50 mg haloperidol as 70.5 mg haloperidol decanoate in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.  
The dose of Haloperidol Decanoate should be expressed in terms of its haloperidol content.  
Store at controlled room temperature 15° to 30°C (59° to 86°F).  
Do not refrigerate or freeze.  
**Protect from light.**  
Dispense in a light-resistant container as defined in the official compendium.  
**CAUTION:** Federal law prohibits dispensing without prescription.

LOT  
EXP

Manufactured by:  
Ben Venue Laboratories, Inc.  
Bedford, OH 44148

**BEDEKORD**  
LABORATORIES<sup>SM</sup>

Manufactured by:  
Bedford Laboratories<sup>SM</sup>  
Bedford, OH 44148

**HALOPERIDOL  
DECANOATE INJECTION**

10 X 1 mL VIALS

NDC 55390-412-01

50 mg/mL\*

**BEDEKORD**  
LABORATORIES<sup>SM</sup>

NO  
PRINT

APPROVE

Format ↑  
■ Black  
■ 2851

**HALOPERIDOL DEC**

50 mg/mL

FOR IM U  
SIF



NDC 55390-412-01

Steri

FOR IM US

6w 05

**HALOPERIDOL DEC**

NDC 55390-01

Insert:  
1 benzyl alcohol as a preservative.  
2 should be expressed in terms of its  
10 to 15° to 30° C (59° to 86° F).

ster as defined in the official compendium  
dispensing without prescription.

**BEDFORD**  
LABORATORIES

Manufactured by:  
Bedford Laboratories™  
Bedford, OH 44116

1 1/2

3 4

Format Number 187A

Black

285 Blue

10 X 1 mL VIALS

**HALOPERIDOL**  
DECANOATE INJECTION

50 mg/mL\*

**BEDFORD**  
LABORATORIES

NO  
PRINT

**APPROVE**

NDC 55390-412-01

10 X 1 mL VIALS

**HALOPERIDOL DECANOATE INJECTION**

50 mg/mL\*

FOR IM USE ONLY

Sterile

**BEDFORD**  
LABORATORIES

HALCA00



NO  
PRINT

10 X 1 mL VIALS

**HALOPERIDOL**  
DECANOATE INJECTION

50 mg/mL\*

**BEDFORD**  
LABORATORIES

1 1/2

2

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER** 074811

**CHEMISTRY REVIEW(S)**

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-811

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories  
300 Northfield Rd  
Bedford OH 44146

4. LEGAL BASIS FOR SUBMISSION

The firm has indicated that to the best of their knowledge, there is no patent in effect for McNeil, by the US patent and Trademark Office for the reference listed drug, and there is no exclusivity in effect.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Haloperidol Decanoate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 12/21/95 ✓  
Amendment 5/14/97 ✓  
Amendment 11/21/97 ✓

10. PHARMACOLOGICAL CATEGORY

Antipsychotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

|(b)4 - Confidential|

13. DOSAGE FORM

Sterile injectable

14. POTENCY

50 mg/mL; 1 mL/vial, 5 m/vial

15. CHEMICAL NAME AND STRUCTURE

4-[4-(p-chlorophenyl)-4-hydroxypiperidino]4'-fluorobutyrophenone decanoate

16. RECORDS AND REPORTS

17. COMMENTS

micro is acceptable 6/20/97.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable - pending method validation.

19. REVIEWER:

DATE:

Nashed E. Nashed, Ph.D.

12/4/97

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 74-811  
Division File  
Field Copy

Endorsements:

HFD-627/N.Nashed, Ph.D./12-4-97 (b)4 - 2/17/97  
HFD-627/P.Schwartz, Ph.D./12-4-97; infiden. 2/17/97  
X:\NEW\FIRMS\AMBEDFORD\LTRS&REV\74-811.3  
F/T by:- bc/12-17-97

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER**            **074811**

**BIOEQUIVALENCE REVIEW(S)**

MAY 8 1996

Haloperidol Decanoate Injection  
50 mg/ml in 1 ml & 5 ml vials  
NDA #74-811  
Reviewer: J. Lee  
74811W.D95

Bedford Laboratories  
A Division of Ben  
Venue Laboratories  
Submission date:  
December 21, 1995

Review of a Request for Waiver

The company has submitted an application for haloperidol decanoate injection 50 mg/ml and is requesting a waiver for in-vivo studies based on 21 CFR 320.22 (b)(1). The drug product is an oil solution intended for IM use that the company claims contain active and inactive ingredients in the same concentration as the brand product, Haldol Decanoate<sup>®</sup> 50 (McNeil Pharmaceutical).

A formulation comparison is presented below:

	<u>Bedford</u> per ml	<u>Haldol</u> per ml
Haloperidol decanoate (base equivalent)	50 mg	50 mg
Benzyl alcohol	1.2%	1.2%
Sesame oil	q.s.	q.s.

Recommendation

1. The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that haloperidol decanoate 50 mg/ml injection falls under 21 CFR 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Bedford's test product is deemed bioequivalent to Haldol Decanoate<sup>®</sup> 50, manufactured by McNeil Laboratories.

 /S/

5/3/96

J. Lee  
Division of Bioequivalence  
Review Branch II

RD INITIALED SNERURKAR  
FT INITIALED SNERURKAR

 /S/

5/3/1996

DIVISION OF CHEMISTRY I.  
OFFICE OF GENERIC DRUGS

Microbiologist's Review #2

June 6, 1997

A. 1. ANDA: 74-811

APPLICANT: Bedford Laboratories  
A Division of Ben Venue Laboratories, Inc.  
Attention: Robert V. Kasubick  
300 Northfield Road  
Bedford, Ohio 44146

2. PRODUCT NAMES: **Haloperidol Decanoate Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

21  
**50 mg/mL** sterile solution; 1 mL fill contained in a 2 cc single dose glass vial and 5 mL fill in a 5 cc multiple dose glass vial for intramuscular injection only

4. METHOD(S) OF STERILIZATION: (b)4 - Confidential

5. PRINCIPLE INDICATIONS: For prolonged parenteral antipsychotic therapy

6. PHARMACOLOGICAL CATEGORY: Antipsychotic drug

B. 1. DATE OF INITIAL SUBMISSION: **December 21, 1995**

2. DATE OF AMENDMENT:

**May 14, 1997 (Received by OGD on 5/15/97)**

**- Subject of this Review**

3. RELATED DOCUMENTS:

**NDA 18-701** held by McNeil Pharmaceutical for the innovator drug product, **Haldol®**

(b)4 - Confidential Business

4. ASSIGNED FOR REVIEW: June 5, 1997

C. REMARKS: The information provided in the amendment was sufficient to determine that the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Haloperidol Decanoate Injection).

D. CONCLUSIONS: The submissions are therefore now recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes."

[Redacted] /S/

6/6/97

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel  
drafted by: KHMuhvich, 6/6/97

cc:

[Redacted] /S/

Original ANDA 74-811  
Field Copy