CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-440

Name: Haloperidol Decanoate Injection, 50 mg (base)/mL and 100 mg (base)/mL, packaged in multiple-dose vials

Sponsor: Apotex Corp.

Approval Date: February 28, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

APPROVAL LETTER

ANDA 75-440

FEB 28 2000

Apotex Corp.
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

This is in reference to your abbreviated new drug application dated August 12, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Haloperidol Decanoate Injection, 50 mg (base)/mL, and 100 mg (base)/mL, packaged in multiple-dose vials.

Reference is also made to your amendments dated April 14, May 19, August 20, September 2, November 8, November 9, December 16, and December 20, 1999; and January 13, January 26, and February 2, 2000.

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 and 100 mg (base)/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Haldol Decanoate-50 Injection, and Haldol Decanoate-100 Injection, respectively, of R. W. Johnson Pharmaceutical Research Institute).

Under section 506A of the Act, 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 and 314.98. 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 that 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-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

2/28/00

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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

Ltr reformatted
RW

cc: ANDA 75-440
Division File
FIELD COPY
HFD-610/R.West
HFD-92
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Endorsements:
HFD-623/N.Takiar/ N. Takiar 2/8/00
HFD-623/D.Gill/ DSGill 2-8-2000
HFD-617/R.Yu/2/8/00 Ryu 2/8/00
HFD-640/A.High/ L. Enoch (for A. High) 2/8/00
HFD-613/D.Catterson/ for D. Catterson 2/8/00 2/8/00
HFD-613/J.Grace/ 2/8/2000

V:\FIRMSAM\APOTEX\LTRS&REV\75440.AP.doc
F/T by: 2/8/00

APPROVAL

Robert Lumpkin
2/28/00

RW 2/28
is pending for minor review
2/29/2000

Mtg held 2/24/00
HFD-610 in concurs with approval
RW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

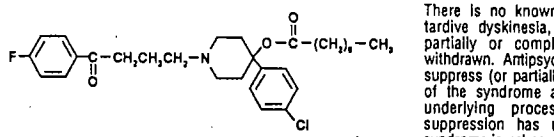
APPROVED LABELING

ENLARGED TO 110%
BY FDA STAFF

Haloperidol Decanoate Injection
For IM Injection Only
R 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. Chemically, haloperidol decanoate is 4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone decanoate. The molecular formula is $C_{31}H_{41}ClFNO_3$. The structural formula is:



Haloperidol decanoate is almost insoluble in water (0.01 mg/ml), but is soluble in most organic solvents. It has a molecular weight of 530.13.

Each mL of Haloperidol Decanoate Injection, 50 mg/mL contains 50 mg haloperidol (present as haloperidol decanoate 70.5 mg) in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

Each mL of Haloperidol Decanoate Injection, 100 mg/mL contains 100 mg haloperidol (present as haloperidol decanoate 141 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 3 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, 50 mg/mL and 100 mg/mL are 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 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 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, 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 cytogenic 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.

FEB 28 2000

Pediatric Use:

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

ADVERSE REACTIONS

Adverse reactions following the administration of Haloperidol Decanoate Injection 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 with haloperidol decanoate 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 the 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, if 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 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 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 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 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 Injection 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) Elderly or Debilitated	10-15 x Daily Oral Dose	10-15 x Previous Daily Oral Dose
High dose Risk of relapse Tolerant to oral haloperidol	20 x Daily Oral Dose	10-15 x Previous Daily Oral Dose

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, 50 mg haloperidol as 70.5 mg per mL haloperidol decanoate in 5 mL multiple dose vials.

Haloperidol Decanoate Injection, 100 mg/mL, 100 mg haloperidol as 141 mg per mL haloperidol decanoate in 5 mL multiple dose vials.

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

Protect from light. Retain vial in carton until contents are used.

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Rev. 07/99 24650020

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

For IM Use Only

5 mL Multiple Dose Vial

℞ only

APOTEX CORP.

USUAL DOSAGE: See package insert.

* Each mL contains 70.5 mg haloperidol decanoate, equivalent to 50 mg haloperidol, 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 15-30°C (59-86°F). Do not refrigerate or freeze. Protect from light. Retain vial in carton until contents are used.

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Mfg for:
Apotex Corp.
Vernon Hills, IL 60061

24655310

FEB 28

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

For IM Use Only

5 mL Multiple Dose Vial

℞ only

APOTEX CORP.

USUAL DOSAGE: See package insert.

* Each mL contains 70.5 mg haloperidol decanoate, equivalent to 50 mg haloperidol, 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 15-30°C (59-86°F). Do not refrigerate or freeze. Protect from light. Retain vial in carton until contents are used.

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Mfg for:
Apotex Corp.
Vernon Hills, IL 60061

24655310

FEB 28

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

For IM Use Only

5 mL Multiple Dose Vial

℞ only

APOTEX CORP.

USUAL DOSAGE: See package insert.

* Each mL contains 141 mg haloperidol decanoate, equivalent to 100 mg haloperidol, 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 15-30°C (59-86°F). Do not refrigerate or freeze. Protect from light. Retain vial in carton until contents are used.

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Mfg for:
Apotex Corp.
Vernon Hills, IL 60061

24665310

FEB 28

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

For IM Use Only

5 mL Multiple Dose Vial

℞ only

APOTEX CORP.

USUAL DOSAGE: See package insert.

* Each mL contains 141 mg haloperidol decanoate, equivalent to 100 mg haloperidol, 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 15-30°C (59-86°F). Do not refrigerate or freeze. Protect from light. Retain vial in carton until contents are used.

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Mfg for:
Apotex Corp.
Vernon Hills, IL 60061

24665310

ENLARGED TO 135%
BY FOIA STAFF

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

5 mL
MULTIPLE DOSE VIAL

℞ Only

Mfg by: Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2
Mfg for: Apotex Corp.
Vernon Hills, IL 60061

Usual Dosage: See package insert.

***Each mL contains:** 70.5 mg haloperidol decanoate, equivalent to 50 mg haloperidol, 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°-30°C (59°-86°F). Do not refrigerate or freeze.

Protect from light. Retain vial in carton until contents are used.

FOR POSITION

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

5 mL MULTIPLE DOSE VIAL

℞ Only

APOTEX CORP.

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

5 mL
MULTIPLE DOSE VIAL

℞ Only

24655330

NDC 60505-0702-1

Haloperidol Decanoate Injection

50 mg/mL*

FOR IM USE ONLY
5 mL
MULTIPLE DOSE VIAL

℞ Only

APOTEX CORP.

OPEN OTHER END

ENLARGED TO 135%

BY FDA STAFF

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

5 mL
MULTIPLE DOSE VIAL

℞ Only

Mfg by: Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2
Mfg for: Apotex Corp.
Vernon Hills, IL 60061

APOTEX CORP.

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

FOR IM USE ONLY
5 mL MULTIPLE DOSE VIAL
℞ Only

Usual Dosage: See package insert.

***Each mL contains:** 141 mg haloperidol decanoate, equivalent to 100 mg haloperidol, 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°-30°C (59°-86°F). Do not refrigerate or freeze.

Protect from light. Retain vial in carton until contents are used.

FOR POSITION

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

5 mL
MULTIPLE DOSE VIAL

℞ Only

FEB 28 24665330

NDC 60505-0703-1

Haloperidol Decanoate Injection

100 mg/mL*

FOR IM USE ONLY
5 mL
MULTIPLE DOSE VIAL

℞ Only

APOTEX CORP.

OPEN OTHER END

ENLARGED TO 135%
BY FOIA STAFF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-440 Date of Submission: August 12, 1998

Applicant's Name: Apotex Corporation

Established Name: Haloperidol Decanoate Injection, 50 mg*/mL and 100 mg*/mL (as haloperidol)

Labeling Deficiencies:

1. CONTAINER (5 mL multiple dose vials)

   a. Increase prominence of the established name and strength to appear as the most prominent information on the label.

   b. Revise the "Each mL contains" statement to read, *Each mL contains mg haloperidol decanoate, equivalent to xx mg haloperidol, in a …

   c. Include the following with the "Protect from light" statement: Retain vial in carton until contents are used.

   d. Ensure that the "5 mL" ——————— appear prominently.

   e. For your 100 mg/mL product, you submitted labels for a ——— multiple dose vial. However, in the HOW SUPPLIED section of your insert labeling and in the Container Closure section (XIV) of your application, you indicate that this product will be packaged in a 5 mL multiple dose vial. Please revise and/or comment.

   f. We encourage you to use boxing, contrasting colors, or other means to differentiate the strength of your products.

2. CARTON (5 mL)

   See CONTAINER comments.

3. INSERT

a. DESCRIPTION

Enhance the readability of your structural formula.

b. CLINICAL PHARMACOLOGY

Revise the first sentence to read,
Haloperidol decanoate is the long…

c. CONTRAINDICATIONS

Change the first paragraph to read,
…decanoate injection are attributed to haloperidol as the active medication, **CONTRAINDICATIONS, WARNINGS,** and additional…

d. PRECAUTIONS

i. Revise the first and sixth paragraphs to delete ——————————.

ii. Carcinogenesis, Mutagenesis, and Impairment of Fertility

A) Revise the subsection heading to delete "and".

B) The ultimate sentence of the first paragraph should read, "cytogenic" rather than ——————.

C) Revise so that the third sentence of the third paragraph, "Antipsychotic drugs elevate…", begins a new paragraph.

e. ADVERSE REACTIONS

i. Revise the first paragraph to delete ——————————.

ii. Tardive Dyskinesia

Combine the ultimate and penultimate paragraphs to read,
…may be masked. It has been reported…

f. DOSAGE AND ADMINISTRATION

i. Delete [redacted] from the first, third and fourth paragraphs.

ii. Revise the second paragraph so that the penultimate sentence, "Close clinical supervision…", begins a new paragraph.

iii. Change the ultimate sentence of the fourth paragraph of your submission to read, experience suggests that… (add "s").

g. HOW SUPPLIED

See CONTAINER comments (c) and (e).

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. This product is light sensitive and packaged in clear, Type I glass. Does the proposed carton adequately protect the product from light?

FOR THE RECORD:

1. Labeling review based on the listed reference drug (Haldol® Decanoate 50 and 100; McNeil Pharmaceutical; revised 10/13/92; approved 4/27/93.)

2. Packaging
Haldol Decanoate 50 is packaged in 10 x 1 mL ampules, 3 x 1 mL amps, and 5 mL multiple dose vials. The 100 mg product is packaged in 5 x 1 mL ampules and 5 mL multiple dose vials.

The applicant is proposing to package its products in 5 mL multiple dose Type I, clear glass vials.

Since this product is light sensitive, Apotex has been asked to include the directive of retaining the vial in the carton until contents are used.

3. Labeling
Since the labeling submission is in draft, the firm has been asked to ensure that the established name and strength appear as the most prominent information on the label; that the vial size is enhanced; and that the products strengths be differentiated.

4. Inactive Ingredients
There does not appear to be a discrepancy in inactives between the DESCRIPTION section of the insert labeling and the C&C Statements.

The product contains benzyl alcohol as a preservative and is not recommended for use in pediatric patients.

5. USP Issues
NDA - Store at CRT 15-30°C (59-86°F). do not refrigerate or freeze. Protect from light.
ANDA - same as RLD

6. Bioequivalence Issues - Pending

7. Patent/Exclusivity issues - None

Date of Review:
January 13, 1999

Date of Submission:
August 12, 1998

Primary Reviewer:

Date:
1/20/99

Team Leader:

Date:

1/20/99

cc:

ANDA: 75-440
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSAM\APOTEX\LTRS&REV\75440NA1.L.DOC/ldg/1/13/99
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-440

Dates of Submission: April 14, 1999 (draft)
May 13, 1999 (FPL)

Applicant's Name: Apotex Corporation

Established Name: Haloperidol Decanoate Injection, 50 mg*/mL and 100 mg*/mL (as haloperidol)

Labeling Deficiencies:

1. CONTAINER (5 mL multiple dose vials)

   a. 50 mg/mL - Revise "Each mL contains ——— mg..." to read "Each mL contains 70.5 mg..." to be consistent with your "Components and Composition" statement on page 142 of your August 31, 1998 submission.

   b. 100 mg/mL - Revise "Each mL contains ——— mg..." to read "Each mL contains 141 mg..." to be consistent with your "Components and Composition" statement on page 143 of your August 31, 1998 submission.

   c. Both strengths - To be consistent with the reference listed drug, we encourage you to insert "For Intramuscular Use Only" after the sentence "The dose of Haloperidol Decanoate should be expressed in terms of its haloperidol content.".

2. CARTON (5 mL)

   a. 50 mg/mL - Revise "Each mL contains ——— mg..." to read "Each mL contains 70.5 mg..."

   b. 100 mg/mL - See comment 1(b) under CONTAINER.

   c. See comment 1(c) under CONTAINER.

3. INSERT

   a. DESCRIPTION

i. Revise the chemical name from "4-[4-(p-chlorophenyl)-4-hydropiperidino]..." to read "4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]..." (See the USP Dictionary of USAN and International Drug Names, 1995 Edition, page 324.)

ii. For the "Each ml..." statements in the third and last paragraphs, see comments 1(a) and 1(b) under CONTAINER.

b. HOW SUPPLIED

See CONTAINER comments 1(a) and 1(b).

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based on the listed reference drug (Haldol® Decanoate 50 and 100; McNeil Pharmaceutical; revised 10/13/92; approved 4/27/93.)

2. Packaging
Haldol Decanoate 50 is packaged in 10 x 1 mL ampules, 3 x 1 mL amps, and 5 mL multiple dose vials. The 100 mg product is packaged in 5 x 1 mL ampules and 5 mL multiple dose vials.

The applicant is proposing to package its products in 5 mL multiple dose Type I, clear glass vials.

Since this product is light sensitive, we had asked Apotex to include the directive of retaining the vial in the carton until contents are used.

3. Active Ingredients -
The statement of content of haloperidol decanoate per each mL, throughout the insert labeling and the container and carton labels for both strengths, is not consistent with the firm's "Components and Composition" statements on pages 142 and 143 of their August 31, 1998 submission (Vol. B1.1). I have asked the firm to revise their labels and labeling accordingly.

4. Inactive Ingredients
There does not appear to be a discrepancy in inactives between the DESCRIPTION section of the insert labeling and the C&C Statements.

The product contains benzyl alcohol as a preservative and is not recommended for use in pediatric patients.

5. Chemical Name -
I have asked the firm to correct the chemical name of haloperidol decanoate to be in agreement with the USP Dictionary of USAN and International Drug Names, 1995 Edition, page 324.)

6. USP Issues
NDA - Store at CRT 15-30°C (59-86°F). do not refrigerate or freeze. Protect from light.
ANDA - same as RLD

7. Bioequivalence Issues - The waiver of an *in vivo* bioequivalent study requirement was granted on October 27, 1998 by the Division of Bioequivalence.

8. Patent/Exclusivity issues - None

Date of Review:
July 13, 1999

Date of Submission:
April 14, 1999 (draft labeling)
May 13, 1999 (FPL)

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 7/21/99

Team Leader: John Grace Date:
John Grace 7/21/1999

cc:

ANDA: 75-440
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review