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
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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

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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

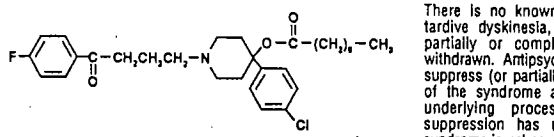
APPROVED LABELING

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)
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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

TAKIAR NEERU 3.1

APPROVAL SUMMARY

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), August 18, 1999 (Fax Amendment), September 2, 1999 (Revised FPL)

Applicant's Name: Apotex Corporation

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER Labels:
50 mg/mL (5 mL vial)
Satisfactory as of September 2, 1999 submission.

100 mg/mL (5 mL vial)
Satisfactory as of September 2, 1999 submission.

CARTON Labeling:
50 mg/mL (5 mL vial)
Satisfactory as of September 2, 1999 submission.

100 mg/mL (5 mL vial)
Satisfactory as of September 2, 1999 submission.

Professional Package Insert Labeling:
Satisfactory as of September 2, 1999 submission.

Revisions needed post-approval: None.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: HALDOL® (haloperidol) Decanoate 50 and 100 injection

NDA Number: 18-701

NDA Drug Name: HALDOL® (haloperidol) Decanoate 50 and 100 injection

NDA Firm: R.W. Johnson (McNeil) Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement : April 27, 1993/S-036

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.

Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
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.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			X
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 p. # 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?[see FTR]		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.		X	
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. **NONE**			

FOR THE RECORD:

1. Labeling review based on the listed reference drug (HALDOL® Decanoate 50 and 100; McNeil Pharmaceutical; NDA 18-701/S-036; 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. Inactive Ingredients:
   There does not appear to be a discrepancy in inactives between the DESCRIPTION section of the insert labeling and the firm's "Components and Composition" statements on pages 142 and 143 of their August 31, 1998 submission (Vol. B1.1).

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

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

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

6. Patent/Exclusivity issues – None.

7. Chemistry – Completed and Acceptable.

8. Microbiology – Pending.

Date of Review:
October 12, 1999

Dates of Submission:
April 14, 1999 (draft), May 13, 1999 (FPL),
August 18, 1999 (Fax Amendment),
September 2, 1999 (Revised FPL)

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 10/13/99

Team Leader: John Grace Date:
John Grace 10/15/1999

Concur: [signature] 10/15/99

cc:

ANDA: 75-440
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:firmsam\apotex\ltrs&rev\75440APL.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.# 1

2. ANDA # 75-440

3. NAME AND ADDRESS OF APPLICANT:

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

4. LEGAL BASIS OF SUBMISSION:

Reference Listed Drugs: **Haldol® Decanoate 50 and**
Haldol® Decanoate 100 (Injections)
Manufacturer: McNeil Pharmaceutical (an R.W. Johnson company)
NDA # 18-701
(Application # N18701 001; Jan 14, 1986; EQ 50 mg base/ml
and # N18701 002; Jan 31, 1997; EQ 100 mg base/ml)

The applicant has certified in their application that in its opinion and to the best of its knowledge, and based upon the published information on the list, the reference listed drug products are not entitled to any patent and exclusivity provisions (v1.1, page 5).

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:

Applicant:

08-31-1998	Correspondence
08-12-1998	Original submission date

FDA:

09-10-1998	ANDA Acceptance letter
08-31-1998	Telecon

08-17-1998 Acknowledge
Debarment Certification: Included section XXI (p 2223)

8. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

11. **Rx or OTC**: Rx

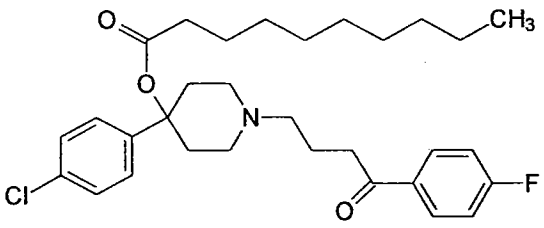
12. **RELATED IND/NDA/DMF(s)**:

Approved NDA 18-701 for innovator
DMF's

13. **DOSAGE FORM**: Injectable

14. **STRENGTH**: 50 mg/mL and 100 mg/mL (5 mL multi-dose vials)

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES**:
Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. 530.12. 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. **COMMENTS**:
The following sections are *NOT SATISFACTORY:*
23. Raw material - active ingredients
26. Manufacturing and Processing
29. Laboratory controls
30. Stability
The following section is *PENDING*
32. Labeling

17. **CONCLUSIONS AND RECOMMENDATIONS**:
The application is not approvable. A MAJOR NA will issue.

18. **RECORDS AND REPORTS**: N/A

19. **REVIEWER**: Neeru B. Takiar **DATE COMPLETED**: 12/18/98
Endorsed by P. Schwartz, Ph.D.

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CHEMISTRY REVIEW #1

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.# 2

2. ANDA # 75-440

3. NAME AND ADDRESS OF APPLICANT:

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

4. LEGAL BASIS OF SUBMISSION:

Reference Listed Drugs: **Haldol® Decanoate 50 and**
Haldol® Decanoate 100 (Injections)
Manufacturer: McNeil Pharmaceutical (an R.W. Johnson company)
NDA # 18-701
(Application # N18701 001; Jan 14, 1986; EQ 50 mg base/ml
and # N18701 002; Jan 31, 1997; EQ 100 mg base/ml)

The applicant has certified in their application that in its opinion and to the best of its knowledge, and based upon the published information on the list, the reference listed drug products are not entitled to any patent and exclusivity provisions (v1.1, page 5).

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:

Applicant:

05-19-1999	Submitted additional information to amendment dated 4/14/99
04-14-1999	Response to deficiency letter dated 1/27/99
02-17-1999	Telecon - Clarification of item 7 in deficiency letter dated 1/27/99
08-31-1998	Correspondence
08-12-1998	Original submission date

FDA:

01-27-1999	Deficiency letter - Major Amendment
09-10-1998	ANDA Acceptance letter
08-31-1998	Telecon
08-17-1998	Acknowledge

Debarment Certification: Included section XXI (p 2223)

8. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

11. **Rx or OTC**: Rx

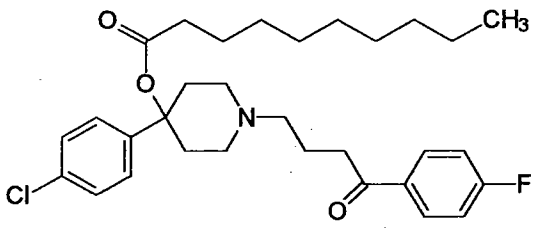
12. **RELATED IND/NDA/DMF(s)**:

Approved NDA 18-701 for innovator
DMF's

13. **DOSAGE FORM**: Injectable

14. **STRENGTH**: 50 mg/mL and 100 mg/mL (5 mL multi-dose vials)

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES**:
Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. 530.12. 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. **COMMENTS**:
The following sections are *NOT SATISFACTORY:*
23. Raw material - active ingredients
29. Laboratory controls
30. Stability
The following sections are *PENDING*
26. Manufacturing and Processing - *Micro*
32. Labeling

17. CONCLUSIONS AND RECOMMENDATIONS:
The application is not Approvable. A Facsimile will issue.

18. RECORDS AND REPORTS: N/A

19. REVIEWER: Neeru B. Takiar
Endorsed by D.Gill, Ph.D.

DATE COMPLETED: 06/08/99
Revised: 07/07/99

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CHEMISTRY REVIEW #2

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NO.# 3**

2. **ANDA #** 75-440

3. **NAME AND ADDRESS OF APPLICANT:**
Apotex Corp.
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. **LEGAL BASIS OF SUBMISSION:**
Reference Listed Drugs: **Haldol® Decanoate 50 and**
Haldol® Decanoate 100 (Injections)
Manufacturer: McNeil Pharmaceutical (an R.W. Johnson company)
NDA # 18-701
(Application # N18701 001; Jan 14, 1986; EQ 50 mg base/ml
and # N18701 002; Jan 31, 1997; EQ 100 mg base/ml)

The applicant has certified in their application that in its opinion and to the best of its knowledge, and based upon the published information on the list, the reference listed drug products are not entitled to any patent and exclusivity provisions (v1.1, page 5).

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:**
Applicant:

11-16-1999	Stability statement for extension of expiry date submitted.
11-08-1999	Additional information submitted in response to telecon dated 10/21/99
08-18-1999	Response to deficiency letter of 7/22/99
05-19-1999	Additional information to amendment of 4/14/99
04-14-1999	Response to deficiency letter dated 1/27/99
02-17-1999	Telecon - Clarification of item 7 in deficiency letter dated 1/27/99
08-31-1998	Correspondence
08-12-1998	Original submission date

FDA:

11-16-1999	Telecon - Additional information requested (Stability)
10-21-1999	Telecon - Additional information requested (Test data)
07-22-1999	Deficiency letter - FACSIMILE
01-27-1999	Deficiency letter - Major Amendment
09-10-1998	ANDA Acceptance letter
08-31-1998	Telecon
08-17-1998	Acknowledge

Debarment Certification: Included section XXI (p 2223)

8. **PHARMACOLOGICAL CATEGORY:** Antipsychotic

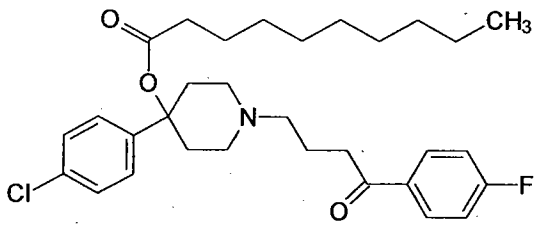
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Approved NDA 18-701 for innovator
DMF's ———————

13. **DOSAGE FORM:** Injectable

14. **STRENGTH:** 50 mg/mL and 100 mg/mL (5 mL multi-dose vials)

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:**
Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. 530.12. 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. **COMMENTS:**
The following section is *DEFICIENT:*
26. Manufacturing and Processing - ***Micro***

17. **CONCLUSIONS AND RECOMMENDATIONS:** The application is Approvable *except MICRO.*

18. **RECORDS AND REPORTS:** N/A

19. **REVIEWER:** Neeru B. Takiar **DATE COMPLETED:** 09/16/99
Endorsed by D. Gill, Ph.D. Revised: 11/18/99

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CHEMISTRY REVIEW #3

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NO.# 4**

2. **ANDA #** 75-440

3. **NAME AND ADDRESS OF APPLICANT:**
Apotex Corp.
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. **LEGAL BASIS OF SUBMISSION:**
Reference Listed Drugs: **Haldol® Decanoate 50 and**
Haldol® Decanoate 100 (Injections)
Manufacturer: McNeil Pharmaceutical (an R.W. Johnson company)
NDA # 18-701
(Application # N18701 001; Jan 14, 1986; EQ 50 mg base/ml
and # N18701 002; Jan 31, 1997; EQ 100 mg base/ml)

The applicant has certified in their application that in its opinion and to the best of its knowledge, and based upon the published information on the list, the reference listed drug products are not entitled to any patent and exclusivity provisions (v1.1, page 5).

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:**
Applicant:

01-28-2000	Additional infor. for response submitted on 1/26/00
01-26-2000	Information submitted in response to telecon dated 01/03/00
11-16-1999	Stability statement for extension of expiry date submitted.
11-08-1999	Additional information submitted in response to telecon dated 10/21/99
08-18-1999	Response to deficiency letter of 7/22/99
05-19-1999	Additional information to amendment of 4/14/99
04-14-1999	Response to deficiency letter dated 1/27/99
02-17-1999	Telecon - Clarification of item 7 in deficiency letter dated 1/27/99

08-31-1998	Correspondence
08-12-1998	Original submission date

FDA:

01-03-2000	Telecon - Additional information requested
11-16-1999	Telecon - Additional information requested (Stability)
10-21-1999	Telecon - Additional information requested (Test data)
07-22-1999	Deficiency letter - FACSIMILE
01-27-1999	Deficiency letter - Major Amendment
09-10-1998	ANDA Acceptance letter
08-31-1998	Telecon
08-17-1998	Acknowledge

Debarment Certification: Included section XXI (p 2223)

8. **PHARMACOLOGICAL CATEGORY:** Antipsychotic

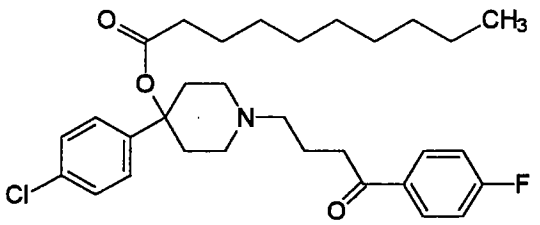
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
Approved NDA 18-701 for innovator
DMF's ———————————

13. **DOSAGE FORM:** Injectable

14. **STRENGTH:** 50 mg/mL and 100 mg/mL (5 mL multi-dose vials)

15. **CHEMICAL NAME, STRUCTURE AND PHYSICAL PROPERTIES:**
Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. 530.12. 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. **COMMENTS:** N/A

17. **CONCLUSIONS AND RECOMMENDATIONS:**
The application is Approvable (PENDING EER).

18. **RECORDS AND REPORTS:** N/A

19. **REVIEWER:** Neeru B. Takiar **DATE COMPLETED:** 02/04/00
Endorsed by D. Gill, Ph.D.

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CHEMISTRY REVIEW #4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

BIOEQUIVALENCE REVIEW(S)

Haloperidol Decanoate Injection
50 mg/ml & 100 mg/ml;
5 mL ——— Vials
ANDA # 75-440
Reviewer: Patrick E. Nwakama
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Apotex Corp.
Vernon Hills, Illinois
Submission Date:
August 12, 1998

Review of a Bioavailability/Bioequivalence Waiver Request

BACKGROUND

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Haloperidol Decanoate injection, 50 mg/mL and 100 mg/mL (5 mL ——— — multi-dose vials). The referenced listed drug (RLD) is Haldol[R] Decanoate 50 mg & 100 mg injections (R.W Johnson Pharmaceutical Research Institute, NDA 18-701, approved 01/14/86 and 01/31/97, respectively).

2. The drug is indicated for use in the management of patients requiring prolonged parenteral antipsychotic therapy (e.g. patients with chronic schizophrenia).

FORMULATION COMPARISON

Comparative compositions of the test and the reference products are as follows:

Formulation Comparison (mg/mL)				
Ingredient	**Test Product**	**RLD**	**Test Product**	**RLD**
Haloperidol Decanoate	70.5*	70.52*	141.0**	141.04**
Benzyl Alcohol, NF	12.0	12.0	12.0	12.0
Sesame Oil	q.s.	q.s.	q.s.	q.s.

* equivalent to 50 mg haloperidol
** equivalent to 100 mg haloperidol

COMMENTS

1. The drug product is classified "AO" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluation."

2. The test drug product contains the same active and inactive ingredients in the same concentrations as the currently approved reference listed product.

3. The waiver of *in vivo* bioequivalent study requirement may be granted based 21 CFR 320.22 (b)(1)of the Bioavailability/ Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Apotex Corp. demonstrates that its Haloperidol Decanoate injection, 50 mg/mL & 100 mg/mL (in 5 mL ——— vials), falls under 21 CFR Section 320.22 (b)(1) of Bioavailability/Bioequivalence regulations. The waiver of *in vivo* Bioequivalence study for Haloperidol Decanoate injection, 50 mg/mL & 100 mg/mL (in 5 mL ——— vials, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Apotex's Haloperidol Decanoate injection, 50 mg/mL & 100 mg/mL (in 5 mL ——— vials)to be bioequivalent to the reference listed product, R.W. Johnson's Haldol^{R}, 50 mg/mL and 100 mg/mL.

Patrick E. Nwakama, Pharm.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR Date: 10/21/1998

Concur Date: 10/27/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS

ANDA: #75-440 APPLICANT: Apotex Corp.

DRUG PRODUCT: Haloperidol Decanoate injection, 50 mg/mL & 100 mg/mL (in 5 mL ——— vials).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-440
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ P. Nwakama

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-655/ P. Nwakama PNW 10/20/98
HFD-655/ S. Nerurkar SAV 10/21/98
HFD-650/ D. Conner DPR 10/27/98

BIOEQUIVALENCY - ACCEPTABLE submission date: August 12, 1998

1. **WAIVER** (WAI) Strengths: 50mg/ml and 100mg/ml
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

OFFICE OF GENERIC DRUGS
Division of Bioequivalence

ANDA#: 75-440 **SPONSOR**: Apotex

DOSAGE FORM: Haloperidol Decanoate Injection in 5 mL _____, vials.
STRENGTH(s): 50 mg/ml & 100 mg/ml
TYPE OF STUDY: N/A
STUDY SITE: N/A

STUDY SUMMARY: N/A

DISSOLUTION: N/A

WAIVER: Waivers of *in vivo* bioequivalence study requirements for 50 mg/ml & 100 mg/ml injections of the test product are granted

---

PRIMARY REVIEWER: Patrick E. Nwakama, Pharm.D. **BRANCH:** II

INITIAL: PEN DATE: 10/20/98

BRANCH CHIEF: Shriniwas G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: DATE: 10/21/1998

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DPC DATE: 10/27/98

DIRECTOR, OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-440

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS
HFD-620
Microbiologists Review #1
September 27, 1999

A. 1. ANDA: **75-440**

APPLICANT: Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAMES: Haloperidol Decanoate

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50mg/mL and 100mg/mL in 5 mL multi-dose vials, for intramuscular injection only

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antipsychotic

B. 1. DATE OF INITIAL SUBMISSION: August 12, 1998
Subject of this Review (Received August 17, 1998)

2. DATE OF AMENDMENT: N/A

3. RELATED DOCUMENTS:
DMF [redacted]

4. ASSIGNED FOR REVIEW: September 14, 1999

C. REMARKS: All review disciplines have completed their review of the application, except microbiology, and have recommended the application for approval with respect to their discipline. The application is pending approval based on conclusion an acceptable microbiology review.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

Lynne A. Ensor 9/27/99
Lynne A. Ensor, Ph. D.

cc: Original **ANDA 75-440**
Duplicate ANDA
Field Copy
Drafted by L. Ensor, HFD 620 v:microrev\75-440
Initialed by A. High and/or M. Fanning

10/5/99

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MICROBIOLOGY REVIEW #1

OFFICE OF GENERIC DRUGS
HFD-620
Microbiologists Review #2
November 29, 1999

A. 1. ANDA: **75-440**

APPLICANT: Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAMES: Haloperidol Decanoate

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50mg/mL and 100mg/mL in 5 mL multi-dose vials, for intramuscular injection only

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Antipsychotic

B. 1. DATE OF INITIAL SUBMISSION: August 12, 1998
(Received August 17, 1998)

2. DATE OF TELEPHONE AMENDMENT: November ~~18~~ 9, 1999
Subject of this Review (Received November 18, 1998)

3. RELATED DOCUMENTS:
DMF ———————

4. ASSIGNED FOR REVIEW: November 24, 1999

C. REMARKS: The subject amendment provides responses to the microbiology deficiencies provided to the applicant in the October 21, 1999 fax.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

Lynne A. Ensor 11/30/99
Lynne A. Ensor, Ph. D.

cc: Original **ANDA 75-440**
Duplicate ANDA
Field Copy

Drafted by L. Ensor, HFD 620 v:microrev\75-440a
Initialed by A. High and/or M. Fanning MF. 12/7/99

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MICROBIOLOGY REVIEW #2

OFFICE OF GENERIC DRUGS, HFD-620
Microbiologists Review #3
December 20, 1999

A. 1. ANDA: **75-440**

APPLICANT: Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAMES: Haloperidol Decanoate

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50mg/mL and 100mg/mL in 5 mL multi-dose vials, IM injection only

4. METHOD(S) OF STERILIZATION: _____

5. PHARMACOLOGICAL CATEGORY: Antipsychotic

B. 1. DATE OF INITIAL SUBMISSION: August 12, 1998
(Received August 17, 1998)

2. DATE OF TELEPHONE AMENDMENTS: November 9, 1999
(Received November 9, 1998)

December 16, 1999
Subject of this Review (Received December 16, 1999)

(Gratuitous Amendment) December 20, 1999
Subject of this Review (Received December 20, 1999)

3. ASSIGNED FOR REVIEW: December 17, 1999

C. REMARKS: The subject amendments provide responses to the microbiology deficiencies provided to the applicant in the December 7, 1999 telephone deficiency letter.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

Lynne A. Ensor 12/20/99
Lynne A. Ensor, Ph. D.

cc: Original **ANDA 75-440**
Duplicate ANDA
Field Copy
Drafted by L. Ensor, HFD-620 v:microrev\75-440a2
Initialed by M. Fanning MF 12/21/99

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #3

OFFICE OF GENERIC DRUGS
HFD-620
Microbiologists Review #4
January 14, 2000

A. 1. ANDA: **75-440**

APPLICANT: Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAMES: Haloperidol Decanoate

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50mg/mL and 100mg/mL in 5 mL multi-dose vials, for intramuscular injection only

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Antipsychotic

B. 1. DATE OF INITIAL SUBMISSION: August 12, 1998

2. DATE OF TELEPHONE AMENDMENTS: November 9, 1999
December 16, 1999

January 13, 2000
Subject of this Review (Received January 13, 2000)

3. RELATED DOCUMENTS: N/A

4. ASSIGNED FOR REVIEW: January 14, 2000

C. REMARKS: The subject amendment provides responses to the microbiology deficiencies provided to the applicant in the December 23, 1999 telephone deficiency letter.

A telecon concerning the remaining microbiology deficiency was held with the firm 1/12/00.

D. CONCLUSIONS: The submission **is recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

Lynne A. Ensor 1/14/00
Lynne A. Ensor, Ph. D.

cc: Original **ANDA 75-440**
Duplicate ANDA
Field Copy
Drafted by L. Ensor, HFD-620 v:microrev\75-440a3
Initialed by M. Fanning 1/18/00

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

ADMINISTRATIVE DOCUMENTS

Telecon

Date: 083198

Time: 1345 H

ANDA #: 75-440

Firm: Apotex Corp.

Drug: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL

Participants: Gregg Davis, FDA and Marcy Macdonald, Apotex

Phone #: 847-573-9999

Agenda:

I called Marcy and asked for some revisions. First, the cover letter states that the strengths are 50 mg/mL and ——mg/mL instead of 50 mg/mL and 100 mg/mL. Second, I asked for a revised 356 H to include all of the block filled out. Lastly, I asked for an explanation of a labeling discrepancy. The package insert states that both strengths will be marketed in a 5 mL vial size only but the 100 mg/mL strength contains container and carton labeling for a —— size only. She said that if the revisions don't involve submitting a new labeling section, she will fax the info and follow with a hard copy. If new labeling is needed, she will send all the info via hard copy only.

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

Reference is made to the firm's fax dated 2/5/99 (attached).

OGD provided the following response to questions contained in the fax.

7c. Testing is necessary. Follow the USP microscopic method.

7d. The spec is for [redacted]. If you do not want to monitor for it, present you rational and evidence that [redacted] is not present for review.

7e. The statement "meet USP <1> requirements" should be present to insure all requirements are met.

Cc:
T-con Binder
ANDA

DATE
2/17/99

ANDA NUMBER
75-440

IND NUMBER

TELECON

FDA Participants
Joe Buccine
Neeru Takiar
Paul Schwartz

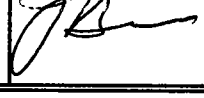
PRODUCT NAME
Haloperidol Dec

FIRM NAME
Apotex Corp.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald
Lenny Rosenberg
Shernay
Lisa Harris

TELEPHONE NUMBER
(847) 573-9999

SIGNATURE
Joe Buccine



APOTEX CORP.

FACSIMILE

To:	Joe Buccine	**Date:** February 5, 1999	
Company:	OGD, FDA	**Fax #**	301-594-0180
From:	Marcy Macdonald	**Pages** (including this page):	
Subject:	Questions Concerning ANDA 75-440		
cc:	847 573 9999 x 223		

Joe:

As per my telephone message, we have several questions concerning the deficiency letter we received 1/27/99 and would appreciate some guidance before we complete our response. Our inquiries are as follows:

7.c.

7.d.

7.e.

We appreciate any assistance in the clarification of these items. I will be contacting you shortly to insure you have received this communication.

Thank you,

Marcy Macdonald

Marcy Macdonald

50 Lakeview Parkway, Suite 127 • Vernon Hills, Illinois 60061 • Tel: 847-573-9999 • Fax: 847-573-1001

x 223

RECORD OF TELEPHONE CONVERSATION

On July 27, 1999, I received a phone call from Marcy McDonald of Apotex Corp. She was calling about the fax of labeling deficiencies we sent them regarding their ANDA 75-440, Haloperidol Decanoate Injection.

Specifically, she asked about Labeling Deficiency "1(c)" under "Container", where I had told them to insert "For Intramuscular Use Only" on the side panel. Marcy did not think it was absolutely necessary because the statement "For IM Use Only" already appears on their front panel.

I spoke with John Grace about it, and he said it would be OK for Apotex to disregard this deficiency "1(c)".

I called Marcy back and informed her that she could ignore "1(c)" and just make a reference to our conversation today in the cover letter of their submission.

Marcy agreed and the telecon ended.

v:\firmsam\apotex\telecons\75440.Jul99.doc

DATE
July 27, 1999

APPLICATION NUMBERS
75-440

IND NUMBER

TELECON

INITIATED BY
_ **APPLICANT/ SPONSOR**
X **FDA**

PRODUCT NAME
Haloperidol Decanoate Injection

FIRM NAME
Apotex Corp.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy McDonald

TELEPHONE NUMBER
847-573-9999 ext. 223

SIGNATURE
Debra M. Catterson
Debra M. Catterson

cc:
ANDA: 75-440
DUP/DIVISION FILE

RECORD OF TELEPHONE CONVERSATION

Reference is made to the firm's fax dated 7/29/99 (attached).

OGD provided the following response to questions contained in the fax.

1. The information provided in the previous amendment refers to the different [redacted]

2. The FDA needs assurance that all of the "Other Requirmenets" stated in the USP Chapter 1 on Injections have been completed and meet the USP specifications.

V:\firmsam\Apotex\telecon\75-440.doc

DATE
July 30, 1999

ANDA NUMBER
75-440

IND NUMBER

TELECON

INITIATED BY: ANDA Holder

PRODUCT NAME
Haloperidol Deconoate

FIRM NAME
Apotex Corp.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy Macdonald, associate director, regulatory affairs

TELEPHONE NUMBER
847-573-9999 x223

SIGNATURE
Ruby Yu 7/30/99

CC: T-Con Binder Log
ANDA 75-440

RECORD OF TELEPHONE CONVERSATION

The firm was contacted concerning the following cmc issues:

1. Please add the statement "Conformance with USP <1> requirements" to the stability specs.
2. Please perform testing, set specs, and submit the data for [redacted] for finished product and stability. The test could be performed on stability samples saved from accelerated stability studies or on room-temperature stability samples to support the proposed expiration period.
3. Please provide the test results of benzyl alcohol for stability samples.

The firm agreed.

The document may be submitted as a Telephone Amendment to Ruby Yu (301) 443-3839 as well as a fax and hard copy to the document room (Document Room Fax number (301) 827-4337).

DATE
October 21, 1999

ANDA NUMBER
75440

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Haloperidol Decanoate

FIRM NAME
Apotex

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald

TELEPHONE NUMBER
847-573-9999 x233

SIGNATURE
Neeru Takiar N. Takiar
Ruby Yu Ryu 10-1-99

V:\firmsam\Apotex\telecon\75440.102199.doc

CC: T-Con Binder Log
ANDA 75-440

RECORD OF TELEPHONE CONVERSATION

The firm contacted OGD concerning the October 21, 1999 t-con.

During the t-con, the firm was asked to perform testing, set specs, and submit the data for ——————— ——— for finished product and stability. The test could be performed on stability samples saved from accelerated stability studies or on room-temperature stability samples to support the proposed expiration period.

The firm called today to inform OGD that they do not have anymore samples saved from accelerated stability studies but do have samples from room temperature stability studies and these samples are approximately 15-16 months old.

The firm was asked to conduct the ——————— tests on the samples from room temperature stability studies. However, the firm was informed that the lack of data from 24-month old samples may hold-up the approval of the ANDA and may require the firm to change their expiration date to less than 24 months.

The firm acknowledged.

DATE
October 29, 1999

ANDA NUMBER
75440

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Haloperidol Decanoate

FIRM NAME
Apotex

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald

TELEPHONE NUMBER
847-573-9999 x233

SIGNATURE
Dave Gill DSG 10-29-99
Ruby Yu RY 11-2-99

V:\firmsam\Apotex\telecon\75440.102999.doc

CC: T-Con Binder Log
ANDA 75-440

RECORD OF TELEPHONE CONVERSATION

The firm was contacted for the following information request:

Regarding the stability protocol, the firm was asked to add a statement to the effect that the same protocol will be used if they decide to extend the expiry date. In addition, the firm will need to submit test results, using the protocol, on a minimum of 3 batches in the annual report.

Firm's response: the requested information will be provided.

DATE
November 15, 1999

ANDA NUMBER
75440

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Haloperidol Decanoate

FIRM NAME
Apotex

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald

TELEPHONE NUMBER
847-573-9999 x233

SIGNATURE
Ruby Yu

V:\firmsam\Apotex\telecon\75440.tc.111599.doc

11-15-99

CC: T-Con Binder Log
ANDA 75-440

RECORD OF TELEPHONE CONVERSATION

The firm was contacted regarding the following CMC issues:

1. Please update and provide the revised COA for the drug substance reflecting the new USP 24 OVI specs.

2. USP 23 and 24 require a specific impurity test for _____. Please revise the drug substance COA to include specs for this impurity or provide a statement that the impurity will not be present when the drug substance is tested, based on a certification from the drug substance manufacturer.

3. Please provide a commitment that the drug product will meet all USP 24 requirements in General Chapter <1>, including those for nonaqueous materials/vehicles.

4. Please include in the stability protocol that the request for extension of the expiration period beyond 24 months must be based on data from a minimum of 3 production batches, using the approved protocol, and the data may be submitted in the annual report.

The firm will provide the requested information within 2 weeks.

DATE
January 3, 2000

ANDA NUMBER
75-440

IND NUMBER

TELECON

INITIATED BY:
FDA

PRODUCT NAME
Haloperidol Decanoate

FIRM NAME
Apotex Corp.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald, Lenny Rosenberg, Sharon Ayd, Lisa McChesney-Hair

TELEPHONE NUMBER
847-573-9999 x223

SIGNATURE
Dave Gill DSG 1-6-00
Neeru Takiar NTakiar 1-6-00
Ruby Yu Dyu 1-6-00

V:\FIRMSAM\APOTEX\TELECONS\75440.tc.010300.doc

CC: T-Con Binder Log
ANDA 75-440

RECORD OF TELEPHONE CONVERSATION

DATE
January 12, 2000

ANDA NUMBER
75440

TELECON

INITIATED BY:
Firm

PRODUCT NAME
Haloperidol Decanoate

FIRM NAME
Apotex

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Marcy MacDonald
Mark Fenton

TELEPHONE NUMBER
847-573-9999 x233

FDA Participants

Andrea High
Lynne Ensor
Joseph Buccine
Ruby Yu

SIGNATURE
[signature] 1-12-2000

The firm requested a t-con with Dr. Ensor, the microbiology reviewer, and Dr. High, the acting team leader, to clarify the deficiency letter that was issued on December 23, 1999.

OGD reiterated that the [redacted] This is a consistent requirement of OGD as well as ONDC. Although the firm states they have an [redacted]

[redacted]

The firm asked if a commitment that during manufacturing, the [redacted] would be an adequate response. OGD said the commitment may be sufficient.

The firm asked about how to submit data on [redacted] after the ANDA has been approved. The supplement may be submitted as CBE-30.

V:\FIRMSAM\APOTEX\TELECONS\75440.TC.011200.DOC

CC: T-Con Binder Log
ANDA 75-440

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-440 Applicant Apotex Corp.
Drug Haloperidol Decanoate Inj Strength 50 mg/mL & 100 mg/mL (as haloperidol)

ROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager Ruby Yu IV
Review Support Br

DRAFT RECEIPT
Date 2/7/00
Initials Ryu

FINAL ACTION
Date
Initials

Application Summary:
Original Rec'd date 8/17/98
Date Acceptable for Filing 8/17/98
Patent Certification (type) II
Date of Office Bio Review 10/27/98
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start End
Commitment Rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☒

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 7/14/99
Date Patent/Exclus.expires N/A
Citizens Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked 2/08/00
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

2. Div. Dir. ~~Deputy Dir.~~ Date 2/9/2000 Date 2/9/2000
Chemistry Div. I ~~or II~~ Initials RC Initials RC
Comments:

The CMC section is satisfactory.

micro issues is pending.

Office Level Chem Review **(1st Generic Only)** Date Date
Chemistry Div. I ~~or II~~ Initials Initials
Comments:

N/A

4. Pat Beers Block Date 2/25/00 Date 2/28/00
Supv., Review Support Branch Initials Initials
RLD = 18-701
EER Status: Acceptable for all facilities as of 7/14/99 (none OAI)

Bioequivalence sites:
Clinical site: N/A
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status:
Analytical site: N/A
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status:

Labeling Status: Acceptable (for 5 ml vial containing 50 mg/mL and 100 mg/mL) as of 10/15/99. No changes to RLD labeling since approval summary.
Bioequivalence office level sign off: Waivers were granted for both the 50 mg/mL and 100 mg/mL strength based on 21 CFR 320.22(d)(2) on 10/27/98
Microbiology status: Sterility assurance review completed and approval recommended 1/4/00
Patent Certification: Para I
Controlled Correspondence/Cit.Pet: N/A
Comments:
MV - acceptable 4/26/99

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issues, Current evaluation for novex is "acceptable"

REVIEWER:

5. Nasser Mahmud
Supv., Reg. Support Branch

DRAFT RECEIPT Date 2/28/00 Initials RW
FINAL ACTION Date 2/28/00 Initials RLWest

Contains certification: Yes ☒ No ☐
(required by the GDEA if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐ No patents
If Para. IV Certification- did applicant
Notify patent holder/NDA holder in a
Timely manner: N/A Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: N/A Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity: Yes ☐ No ☒
Comments:
No unexpired patents or exclusivity.

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity Tracking System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD = Haldol Decanoate - 50
Haldol Decanoate - 100
RW Johnson Pharm Res. Institute
NDA 18-701

6. Robert L. West
Dir. Div. Labeling & Prog. Support
Comments: Acceptable EES dated 7/14/99 (verified 2/25/00). No O.A.I. alerts noted. Bioequivalence waiver granted under 320.22(b)(1) on 10/21/98. Office level bio endorsed 4/27/98 (D. Conner). FPL acceptable for approval 10/15/99. Microbiology/Sterility assurance acceptable 1/18/00. CMC acceptable 2/8/00. Methods validation completed. ____ has been requested for ____. A meeting was held on 2/24/00 in OGD and it was agreed to proceed with approval based upon acceptable EES. Mary Fanning ____. J. Buccine is P.M. of record on this issue.

Date 2/28/00 Initials RW
Date 2/28/00 Initials Robert L West

7. Gary Buehler
Deputy Director, OGD

Date 2/28/00 Initials RW
Date 2/28/00 Initials GBuehler

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments: No unexpired patents or exclusivity. No controlled correspondence or Citizen Petitions currently pending. No pediatric exclusivity issues. O.K. to approve.

8. Douglas L. Sporn
Director, OGD
Comments:

Date 2/28/00 Initials DS
Date 2/28/00 Initials DS

~~Roger Williams, M.D.~~
~~Deputy Center Director for~~
~~Pharmaceutical Science~~
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

Date ____ Initials ____
Date ____ Initials ____

9. Project Manager Ruby Yu
Review Support Branch

Date 2/28/00 Initials RY
Date 2/28/00 Initials RY

(RW) N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:
3:10pm Time notified of approval by phone 3:15pm Time approval letter faxed

FDA Notification:
2/28/00 Date e-mail message sent to "OGD approvals" account
2/28/00 Date Approval letter copied to "//cder/drugapp" directory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-440

CORRESPONDENCE

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX (847) 573-1001

August 12, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL
Original Submission

Dear Mr. Sporn,

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act as amended September 24, 1984, Apotex Corp. hereby submits an abbreviated new drug application for Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL.

We are submitting an archival copy under a blue cover, a chemistry review copy plus an additional copy of the analytical methods section under red covers, and the bioavailability/bioequivalence review section under an orange cover.

Apotex Corp. certifies that, in accordance with 21 CFR 314.94(d)(5), a true field copy of the technical sections of this submission is being provided to the Office of Generic Drugs.

We appreciate your review of this application. Please direct any inquiries regarding this application to me at the address listed.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

J:\ANDA\Haloperidol\origltr.wpd

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

August 12, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL
Bioavailability/Bioequivalence Information

Dear Mr. Sporn,

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act as amended September 24, 1984, Apotex Corp. hereby submits bioavailability/bioequivalence information in support of an abbreviated new drug application for Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL.

Draft labeling, formulation information for the test drug and listed drug, and a request for waiver of any bioavailability/bioequivalence study requirements for Apotex Corp.'s Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL are enclosed.

We appreciate your review of this application. Please feel free to contact me if you have any questions.

Sincerely,

Mary Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

J:\ANDA\Haloperidol\bioltr.wpd

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX (847) 573-1001

August 31, 1998

NEW CORRESP

NC

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA #75-440
Haloperidol Decanoate Injection 50 mg/mL and 100 mg/mL
Original Submission

Dear Mr. Sporn,

Attached are the following revised documents:

1. Revised cover letters
2. Completed Form 356h
3. Haloperidol Decanoate Injection 100 mg/mL revised labeling that now correctly reflects the 5 mL multi-dose vial
4. Revised components and composition for 100 mg/mL

A hard copy will follow by mail which shall include a set for the archive copy and a set for the field copy.

Please feel free to contact me if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

MM/ty

Enclosures

RECEIVED

SEP 0 1 1998

GENERIC DRUGS

ANDA 75-440

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

SEP 10 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated August 31, 1998 and your correspondence dated August 31, 1998.

NAME OF DRUG: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL

DATE OF APPLICATION: August 12, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 17, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joseph Buccine
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips 9/8/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-440
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
Endorsement:
HFD-615/PRickman, Chief, RSB _____ date 9/8/98
HFD-615, GDavis, CSO _____ date 09/03/98
HFD-629, PSchwartz, Sup. Chem. _____ date
WP File x:\new\firmsam\apotex\ltrs&rev\75440.ack
F/T mjl/9/1/98
ANDA Acknowledgment Letter!

MAJOR AMENDMENT

ANDA 75-440

JAN 27 1999

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Apotex Corporation PHONE: 847 573 9999

ATTN: Marcy Macdonald FAX: 847 573 1001

FROM: Joseph Buccine PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile 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*/mL and 100 mg*/mL (as haloperidol).

Reference is also made to your amendment(s) dated .

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (7 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry, labeling and bioequivalency comments are provided.

X:\new\ogdadmin\macros\faxmaj.frm

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

JAN 27, 1999 FDA FAX

b. [ ]

In addition, provide an explantion for test results of description at two and three months testing time points on pages 1882-1884, 1947-1950.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

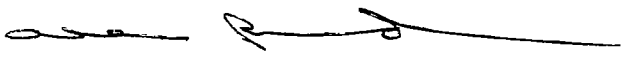
1. The microbiological section of your application is under review. Review comments, if any, will be communicated separately.

2. Method validation from the FDA district laboratory has been requested

3. Please provide all available room temperature stability data.

4. Extension of expiration date requires full term data on three production lots.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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.

John L. Gueffroy

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

BIOEQUIVALENCY COMMENTS

ANDA: #75-440 APPLICANT: Apotex Corp.

DRUG PRODUCT: Haloperidol Decanoate injection, 50 mg/mL & 100 mg/mL (in 5 mL ——— vials).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 14, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

DR. Label

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

NDA ORIG AMENDMENT
AC

To Whom It May Concern:

Apotex Corp. is hereby providing response to the major deficiency letter received January 27, 1999.

We have responded to each item individually as presented in the deficiency letter. Labeling information follows at the end of the chemistry, manufacturing and control responses.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
APR 16 1999
GENERIC DRUGS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

May 13, 1999

NDA ORIG AMENDMENT
N/AF

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

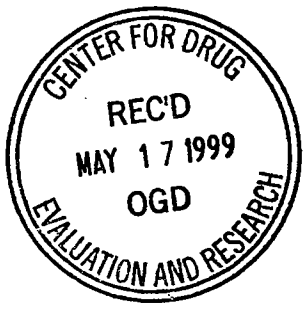
Apotex Corp. is hereby providing 12 sets of final printed labeling. We submitted draft labeling on April 14, 1999, in response to the major deficiency letter dated January 27, 1999 (copy attached). These final labels are the same as the draft labels except for minor placement formatting and removal of the UPC Symbol from the container label.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

May 19, 1999

NDA ORIG AMENDMENT
N/AC

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Additional Information to the Amendment dated April 14, 1999

Re: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby providing additional information to Item 7.d. of the major amendment dated April 14, 1999 for the deficiency received on January 27, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 24 1999
OGD

FACSIMILE AMENDMENT

JUL 22 1999

ANDA 75-440

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Apotex Corp. PHONE: (847) 573-9999 x233

ATTN: Marcy Macdonald FAX: (847) 573-1001

FROM: Ruby Yu PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile 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*/mL and 100 mg*/mL (as haloperidol).

Reference is also made to your amendment(s) dated April 14, May 13, and May 19, 1999.

Attached are 4 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided. Labeling comments also included.

X:\new\ogdadmin\macros\faxfax.frm

7/22/99

JUL 22 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-440 **APPLICANT:** Apotex Corp.

DRUG PRODUCT: Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. [redacted]
2.
3.
4.
5.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The microbiological section of your application is under review. Review comments, if any, will be communicated separately.

2. Please provide all available room temperature stability data.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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.

John D. Grace for

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

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

August 18, 1999

NEW CORRESP
NC to FAX

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

FASCIMILE AMENDMENT

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby providing response to the fascimile deficiency letter dated July 22, 1999 (copy attached). At this time we are submitting draft labeling and will provide final printed labeling as soon as it is available.

We have responded to each item individually as presented in the deficiency letter. This response is being submitted in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

FACSIMILE

To:	Ruby Yu	**Date:** August 20, 1999	
Company:	OGD, CDER, FDA	**Fax #**	301-827-4337
From:	Karen Kasprzycki	**Pages (Including this page):**	224
Subject:	ANDA 75-440 -- Haloperidol Decanoate Injection FACSIMILE AMENDMENT		
cc:			

Attached is the facsimile amendment in response to your deficiency letter dated July 22, 1999 for the above-referenced product.

Please note that this fax does not include multiple copies of the proposed labeling however, the hard copy will include all four copies. We will forward the original document and one copy via the postal service.

Thank you.

FA
[illegible] AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

September 2, 1999

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AF

LABELING AMENDMENT

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby providing 12 sets of final printed labeling. We submitted draft labeling on August 18, 1999, in response to the facsimile deficiency letter dated July 22, 1999 (copy attached).

The container labels and cartons are the same as those submitted in draft format. The only additional change made to the insert is that the Apotex Corp. address was removed from the end to allow for private label distribution. A comparison page is included.

This amendment is being submitted in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald (KK)

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 443-3839

FAX TRANSMISSION COVER SHEET

Date:	October 21, 1999
To:	Marcy MacDonald, Apotex Corp.
Fax:	847-573-1001
Re:	ANDA 75-440
Sender:	Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: __5___
(Excluding Cover Sheet)

SPECIAL INSTRUCTIONS:

Microbiology comments are provided. Your response may be labeled as "Telephone Amendment". Please fax a copy of your response to me at 301-443-3839 followed by hard-copies to the document room.

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

FDA FAX 10/21/1999

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

November 8, 1999

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/FA

RESPONSES TO TELEPHONE CONVERSATION DEFICIENCIES
(October 21, 1999)

RE: ANDA 75-440
Haloperidol Decanoate for Injection, 50mg/mL and 100mg/mL

To Whom It May Concern:

As per the telephone conversation (10/21/99) between Marcy Macdonald, Ruby Yu and Dr. David Gill of the Office of Generic Drugs, we are providing the requested information.

Please feel free to contact me if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX: (847) 573-1001

November 9, 1999

ORIG AMENDMENT

NIFA

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby submitting in duplicate a response to the telephone deficiency letter dated October 21, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX (847) 573-1001

November 16, 1999

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

Re: ANDA 75-440
Haloperidol Decanoate Injection 50 mg/mL & 100 mg/Ml

As per the telephone conversation between Marcy Macdonald of Apotex Corp. and Ruby Yu, Office of Generic Drugs, we are providing the following certification:

We will use the same approved stability protocol (as previously filed on November 08, 1999) to extend the expiration date of the product. For such an extension, room temperature stability data will be provided (as per the approved protocol) for 3 different lots of product and filed in the annual report.

Please feel free to contact me if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 443-3839 / 301 594-0180

FAX TRANSMISSION COVER SHEET

Date:	December 7, 1999
To:	Marcy MacDonald, Apotex Corp.
Fax:	847-573-1001
Re:	ANDA 75-440
Sender:	Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: __2___
(Excluding Cover Sheet)

SPECIAL INSTRUCTIONS:

Microbiology comments are provided. Your response may be labeled as "Telephone Amendment". Please fax a copy of your response to me at 301-594-0180 followed by hard-copies to the document room.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

December 16, 1999

NEW CORRESP
to Seq

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: ANDA 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby submitting in duplicate a response to the telephone deficiency letter dated December 07, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

December 20, 1999

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

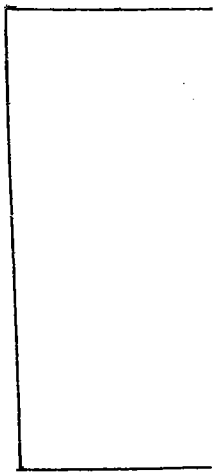
ADDITIONAL INFORMATION FOR
MICRO TELEPHONE AMENDMENT RESPONSE OF
DECEMBER 16, 1999

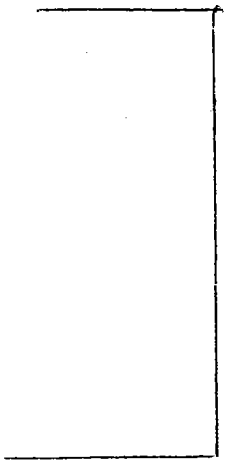
Re: ANDA: 75-440
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

We are writing to provide additional information to clarify our response to item number 3 of our communication dated December 16, 1999.

In our response, we noted that "We do not consider





Please do not hesitate to contact me if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 594-0180

FAX TRANSMISSION COVER SHEET

Date:	December 23, 1999
To:	Marcy MacDonald, Apotex Corp.
Fax:	847-573-1001
Re:	ANDA 75-440
Sender:	Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: __1___
(Excluding Cover Sheet)

SPECIAL INSTRUCTIONS:

Microbiology comments are provided. Your response may be labeled as "Telephone Amendment to Microbiology Deficiency". Please fax a copy of your response to me at 301-594-0180 followed by hard-copies to the document room. In addition, please call me before you fax your response.

Microbiology Comments to be Provided to the Applicant

ANDA: 75-440 APPLICANT: Apotex Corporation

DRUG PRODUCT: Haloperidol Decanoate for Injection (50mg/mL and 100 mg/mL in 5 mL multi-dose vials)

A. Microbiology Deficiencies:

1. [redacted]

Please clearly identify your amendment to this facsimile as "A RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

Mary Fanning, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX. (847) 573-1001

January 13, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT
TO MICROBIOLOGY DEFICIENCY

RE: **ANDA #75-440**
Haloperidol Decanoate for Injection
50 mg/mL and 100 mg/mL in 5 mL multi-dose vials

To Whom It May Concern:

Apotex Corp., a Division of Apotex Inc., is hereby submitting in duplicate a response to the Telephone Amendment To Microbiology Deficiency letter dated December 23, 1999.

Please let me know if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

January 26, 2000

NDA ORIG AMENDMENT
N/FA

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: **ANDA # 75-440**
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL

To Whom It May Concern:

Apotex Corp., a Division of Apotex Inc., is hereby submitting in duplicate a response to a FDA telephone conversation between Apotex Corp. and Ruby Yu, Dr. Gill and Neeru Takiar all from OGD, FDA on January 03, 2000.

Please let me know if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 28 2000
OGD

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

NDA ORIG AMEND

FA

February 2, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ADDITIONAL INFORMATION FOR RESPONSE SUBMITTED JANUARY 26, 2000

RE: **ANDA #75-440**
Haloperidol Decanoate Injection
50 mg/mL and 100 mg/mL in 5 mL multi-dose vials

To Whom It May Concern:

Apotex Corp. is hereby providing additional information for the above referenced ANDA for response #2 noted in our communication of January 26, 2000.

We are attaching additional information from the drug substance manufacturer concerning [redacted]

Please let me know if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs
Ext. 223