CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

Approval Letter

ANDA 75-393

MAY 11 1999

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
17 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application dated May 29, 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 (Single and Multiple-Dose Vials).

Reference is also made to your amendments dated December 16, 1998; and January 12, January 22, March 2, and April 20, 1999.

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 [50 mg (base)/mL], and Haldol Decanoate-100 Injection [100 mg (base)/mL], respectively, of R. W. Johnson Pharmaceutical Research Institute).

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 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 which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-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,

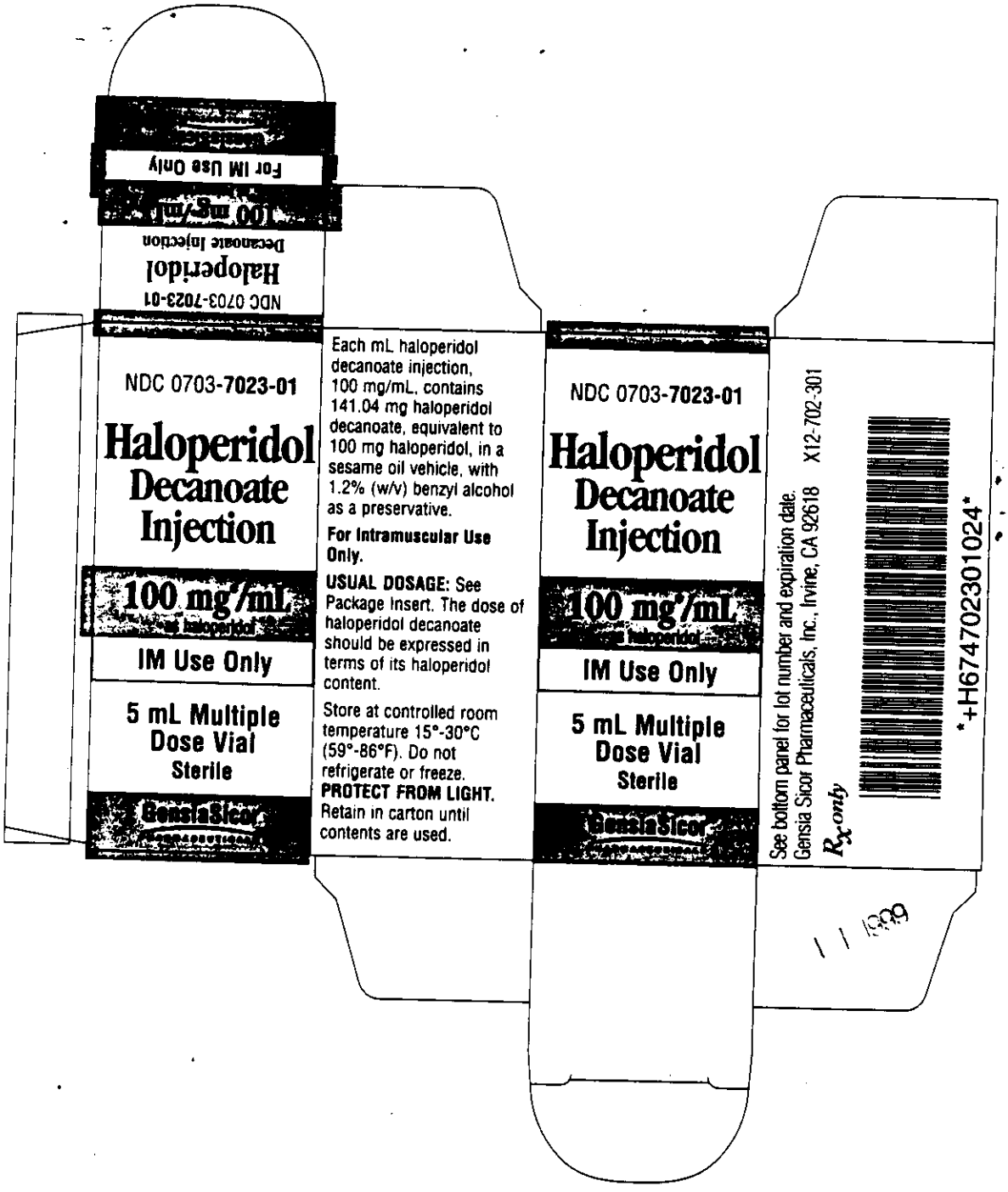
/S/ 1/11/99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

FINAL PRINTED LABELING


NDC 0703-7023-01
Haloperidol
Decanoate Injection
100 mg*/mL
*as haloperidol
IM Use Only
5 mL Multiple Dose Vial
Sterile
GensiaSicor
Each mL haloperidol decanoate injection, 100 mg/mL, contains 141.04 mg haloperidol decanoate, equivalent to 100 mg haloperidol, in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.
For Intramuscular Use Only.
USUAL DOSAGE: See Package Insert. 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 in carton until contents are used.
NDC 0703-7023-01
Haloperidol
Decanoate Injection
100 mg*/mL
*as haloperidol
IM Use Only
5 mL Multiple Dose Vial
Sterile
GensiaSicor
See bottom panel for lot number and expiration date.
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618
X12-702-301
Rx only
+H674702301024

Y36-102-301
Package Insert

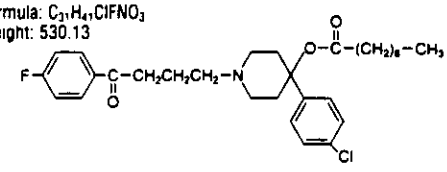
GensiaSicor™ PHARMACEUTICALS

Haloperidol
Decanoate Injection
For IM Injection Only

DESCRIPTION

Haloperidol decanoate is the decanoate ester of the butyrophenone, haloperidol. It has a markedly extended duration of effect. It is available in sesame oil in sterile form for intramuscular (IM) injection. Haloperidol decanoate is 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4 piperidinyl decanoate. The structural formula for haloperidol decanoate is:

Molecular Formula: $C_{31}H_{41}ClFNO_3$
Molecular Weight: 530.13



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

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

Each mL of haloperidol decanoate injection, 100 mg/mL, contains 100 mg haloperidol (present as haloperidol decanoate 141.04 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 haloperidol decanoate injection 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.

Pediatric Use

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

ADVERSE REACTIONS

Adverse reactions following the administration of haloperidol decanoate injection 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 5½ 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 10-15 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 dependant 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

NDC Number	Haloperidol Decanoate Injection, equivalent to haloperidol	Volume
0703-**7011-03**	50 mg/mL	1 mL fill in a 2 mL vial
0703-**7021-03**	100 mg/mL	1 mL fill in a 2 mL vial
0703-**7013-01**	50 mg/mL	5 mL multiple dose vial
0703-**7023-01**	100 mg/mL	5 mL multiple dose vial

2 mL vials are packaged 10 vials per shelf pack.

5 mL multiple dose vials are packaged in single unit cartons.

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

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

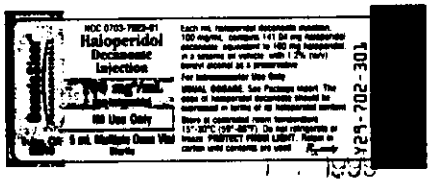
Rx only

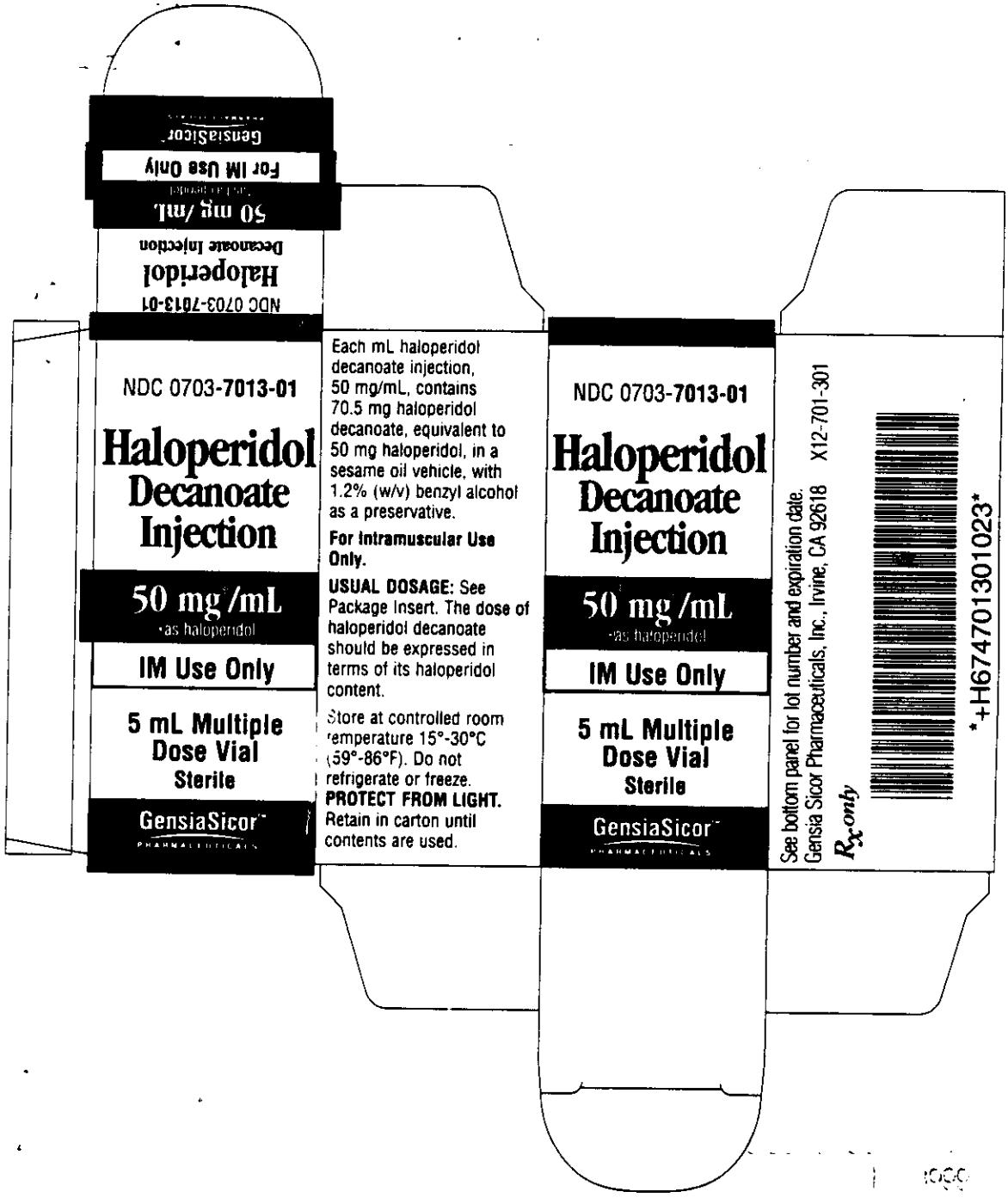
Issued: November 1998
Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA 92618

VIAL LABEL

100 mg/mL, 5 mL fill

Part # Y29-702-301




NDC 0703-7013-01
Haloperidol
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5 mL Multiple Dose Vial
Sterile
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Each mL haloperidol decanoate injection, 50 mg/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.
For Intramuscular Use Only.
USUAL DOSAGE: See Package Insert. 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 in carton until contents are used.
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Haloperidol
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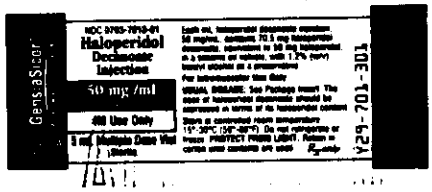
50 mg/mL
as haloperidol
IM Use Only
5 mL Multiple Dose Vial
Sterile
GensiaSicor
See bottom panel for lot number and expiration date.
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618
X12-701-301
Rx only
+H674701301023

VIAL LABEL

50 mg/mL, 5 mL fill

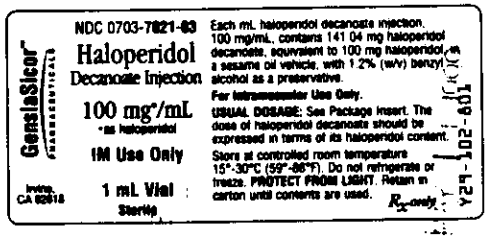
Part # Y29-701-301



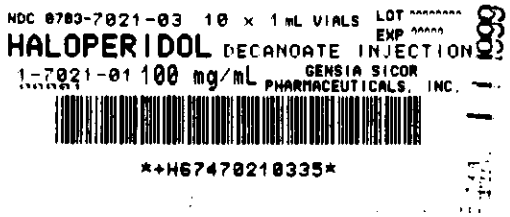
SHELF PACK LABELS

100 mg/mL, 1 mL fill

Part # Y29-102-801



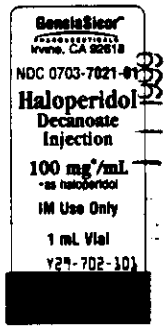
Part # 1-7021-01



VIAL LABEL

100 mg/mL, 1 mL fill

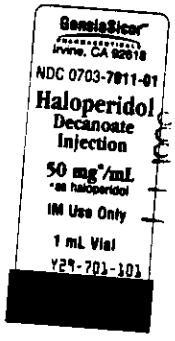
Part # Y29-702-101



VIAL LABEL

50 mg/mL, 1 mL fill

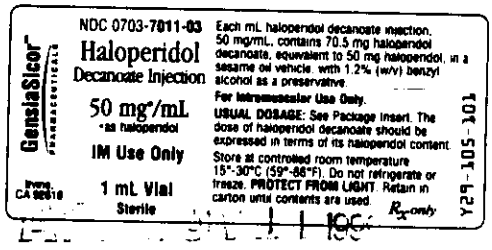
Part # Y29-701-101



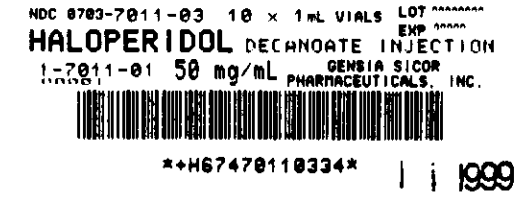
SHELF PACK LABELS

50 mg/mL, 1 mL fill

Part # Y29-105-101



Part # 1-7011-01



CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-393

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in their opinion and to the best of their knowledge there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug referred to in this application.
And there are no unexpired exclusivities exist for RW Johnson's Haldol Decanoate.

5. SUPPLEMENT(s)

Original 5/29/98

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Haloperidol Decanoate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 12/16/98
Telephone amendment: 4/20/99
Micro Amendment: 3/3/99
Labeling amendment: 1/22/99

10. PHARMACOLOGICAL CATEGORY

Antipsychotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's 12530, 1546

13. DOSAGE FORM

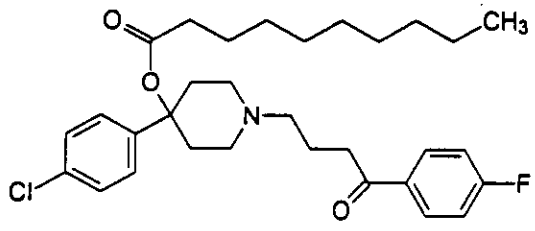
Liquid Injection

14. POTENCY

50 mg Base/ mL and 100 mg Base/ mL

15. CHEMICAL NAME AND STRUCTURE

Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. MW 530.12. Chemical Abstract number 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. RECORDS AND REPORTS

17. COMMENTS

The Microbiology Review is satisfactory on 3/16/99.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 4/22/99

Supervisor: Paul Schwartz, Ph.D. 4/22/99

Page(s) 15

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Chemistry Review #2, 4/22/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-393 APPLICANT: Gensia Scior Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection
50 mg/mL in 1 mL & 5 mL vials
100 mg/mL in 1 mL & 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,

/S/

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

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

AADA # 75-393 **SPONSOR : Gensia Sicor Pharmaceuticals**
DRUG & DOSAGE FORM : Haloperidol Decanoate Injection
STRENGTH (s) : 50 mg/mL in 1 mL and 5 mL vials
100 mg/mL in 1 mL and 5 mL vials
TYPE OF STUDY: SD SDF MULT X OTHER
STUDY SITE: N/A

STUDY SUMMARY : N/A

Formulation: Acceptable
Waiver is granted.

PRIMARY REVIEWER: Jahnavi S. Kharidia, Ph.D. **BRANCH : 3**
INITIAL JSK **DATE :** 9/4/98

TEAM LEADER: Barbara M. Davit, Ph.D. **BRANCH : 3**
INITIAL : BMD **DATE :** 9/8/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL : JS **DATE :** 9/10/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ **DATE :**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-393 APPLICANT: Gensia Scior Pharmaceuticals

DRUG PRODUCT: Haloperidol Decanoate Injection
50 mg/mL in 1 mL & 5 mL vials
100 mg/mL in 1 mL & 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,

/S/

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

CC:

X:\NEW\FIRMSAM\GENSIA\LTRS&REV\75393W.598.DOC
Printed in final on 9/4/98

BIOEQUIVALENCY - ACCEPTABLE submission date: 29 May, 1998

6. **WAIVER** (WAI) Strengths: 50 mg/mL and 100 mg/mL
Outcome: AC

Outcome Decisions: **AC** - Acceptable
WinBio Comments: Waiver is granted

Haloperidol Decanoate Injection
50 mg/mL in 1 mL & 5 mL vials
100 mg/mL in 1 mL & 5 mL vials
ANDA #75-393
Reviewer: Jahnavi S. Kharidia
X:\NEW\FIRMSAM\GENSIA\LTRS&REV\75393W.598.DOC

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine CA 92618
Submission Date:
29 May, 1998

Review of a Waiver Request

Haloperidol decanoate is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral antipsychotic therapy. Innovator products are Haldol® Decanoate 50 and Haldol® Decanoate 100 manufactured by R.W. Johnson Company.

The firm has submitted the application for haloperidol decanoate injection 50 mg/mL and 100 mg/mL and is requesting a waiver of *in vivo* bioavailability requirements based on 21 CFR 320.22 (b)(1).

Formulation:

Ingredient (mg/mL)	Haloperidol Decanoate Injection			
	50 mg/mL		100 mg/mL	
	Gensia Sicor	R.W. Johnson	Gensia Sicor	R.W. Johnson
Haloperidol Decanoate	70.52[1]	70.52[1]	141[2]	141[2]
Benzyl Alcohol,	12.0		12.0	
Sesame Oil,	q.s. to 1.0 mL		q.s. to 1.0 mL	
Nitrogen,	as required		as required	

[1] equivalent to 50 mg Haloperidol
[2] equivalent to 100 mg Haloperidol

Comments:

1. The test product is in a vehicle intended solely for intramuscular administration.

2. The active ingredients, route of administration, dosage form and strengths of the test drug products are the same as those of the reference listed drug.

3. All ingredients in test and reference products are qualitatively and quantitatively the same.

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Gensia Sicor Pharmaceuticals, Inc. demonstrates that haloperidol decanoate injections, 50 mg/mL and 100 mg/mL, fall under 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waivers of the *in vivo* bioequivalence study requirements for 50 mg/mL and 100 mg/mL haloperidol decanoate injections are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test products to be bioequivalent to Haldol® decanoate 50 and Haldol® decanoate 100 manufactured by R. W. Johnson Company, respectively.

Jahnavi S. Kharidia, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED BDAVIT BDM 9/5/98
FT INITIALED BDAVIT _____ Date 9/8/98

Concur: _____ Date 9/10/98

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

cc: ANDA # 75-393 (original, duplicate), Kharidia, HFD-658, Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #3
March 16, 1999

A. 1. **ANDA 75-393**

APPLICANT Gensia Sicor Pharmaceuticals, Inc
17 Hughes
Irvine California 92718-1902

2. PRODUCT NAMES: Haloperidol Decanoate Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg Base/mL in a 1 mL Single Dose 2 mL Vial, 50 mg Base/mL in a 5 mL Multiple Dose, 100 mg Base/mL in a 1 mL Single Dose 2 mL Vial and 100 mL Base/mL in a 5 mL Multiple Dose, Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Anti-psychotic

B. 1. DATE OF INITIAL SUBMISSION: May 29, 1998
(Received June 1,1998)
2. DATE OF FAX AMENDMENT: March 2, 1999
Subject of this Review (Received, March 3, 1999)
3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: 3/16/99

C. REMARKS: The subject amendment is in response to the microbiology deficiencies in the FAX amendment dated February 16, 1999.

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

/S/ 3/16/99
Andrea S. High, Ph. D.

cc:

ev\75-393a2

Page(s) 1

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Commercial/Confidential

Information and are not

releasable.

Microbiology Comments to be Provided to the Applicant

ANDA: 75-393 **APPLICANT: Gensia Sicor**

DRUG PRODUCT: Haloperidol Decanoate Injection USP

Microbiology Deficiency:

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
February 9, 1999

A. 1. **ANDA 75-393**

APPLICANT Gensia Sicor Pharmaceuticals, Inc
17 Hughes
Irvine California 92718-1902

2. PRODUCT NAMES: Haloperidol Decanoate Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg Base/mL in a 1 mL Single Dose 2 mL Vial, 50 mg Base/mL in a 5 mL Multiple Dose, 100 mg Base/mL in a 1 mL Single Dose 2 mL Vial and 100 mL Base/mL in a 5 mL Multiple Dose, Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Anti-psychotic

B. 1. DATE OF INITIAL SUBMISSION: May 29, 1998
(Received June 1,1998)

2. DATE OF FAX AMENDMENT: December 16, 1998
Subject of this Review (Received, December 17, 1998)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 2/9/99

C. REMARKS: The subject amendment is in response to the microbiology deficiencies in the FAX amendment dated December 7, 1998.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/S/

Andrea S. High, Ph. D.

cc:

Page(s) 3

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Microbiologist
Review #2

Microbiology Comments to be Provided to the Applicant

ANDA: 75-393 APPLICANT: Gensia Sicor Pharmaceuticals

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

A. Microbiology Deficiencies:

1. Regarding personnel monitoring, the glove count appears to be excessive.

2. Regarding filtration:

   a. Please specify the minimum acceptable bubble point for the subject drug product(s) as it was not provided in the batch record or stated elsewhere in the ANDA.

   b. Please state the duration for the filtration of the subject drug product(s) during production (maximum batch size).

3. You should include sterility and endotoxin testing at time "0" in your stability protocol.

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

The manufacturing facility address, 19 Hughes, appears on the diagrams and in the text; however, it was stated in Vol. 1.1, p. 100114 that the subject drug product(s) were made at 17 Hughes. The facility address should be clarified.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Banning, M.D., Ph.D.
Assosiate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #1

November 20, 1998

A. 1. ANDA 75-393

APPLICANT Gensia Sicor Pharmaceuticals, Inc
17 Hughes
Irvine California 92718-1902

2. PRODUCT NAMES: Haloperidol Decanoate Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg Base/mL in a 1 mL Single Dose 2 mL Vial, 50 mg Base/mL in a 5 mL Multiple Dose, 100 mg Base/mL in a 1 mL Single Dose 2 mL Vial and 100 mL Base/mL in a 5 mL Multiple Dose, Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Anti-psychotic

B. 1. DATE OF INITIAL SUBMISSION: May 29, 1998
Subject of this Review (Received June 1,1998)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 11/18/98

C. REMARKS: The subject drug product is filled in Room Filling Line at the Irvine California pharmaceutical facility.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments regarding the filling process are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/S/ 1/20/98
Andrea S. High, Ph. D.

cc:

-393

Page(s) 9

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Information and are not

releasable.

Micro Review

#1

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

ADMINISTRATIVE DOCUMENTS

APPLICATION REASSIGNMENT AUTHORIZATION FORM
OFFICE OF GENERIC DRUGS

ANDA/AADA#	DRUG	FIRM
75-393	Haloperidol Decanoate Injection	Dava Sicor Pharmaceuticals

1. REASSIGN FROM: MIC

DATE OF ORIGINAL ASSIGNMENT: _____

2. ASSIGN TO: Andrea High

DATE OF REASSIGNMENT: _____

REASON FOR REASSIGNMENT: _____

/S/
BRANCH SUPERVISOR (SIGNATURE) DATE

CONCUR: ___ NOT CONCUR: ___

CHEMISTRY/BIOEQUIVALENCE
DIVISION DIRECTOR (SIGNATURE) DATE: _____

A COPY OF THIS FORM SHOULD BE PLACED IN EACH APPLICATION AND IN THE DIVISION FILE

APPLICATION REASSIGNMENT AUTHORIZATION FORM
OFFICE OF GENERIC DRUGS

ANDA/AADA#	DRUG	FIRM
75-393	Haloperidol Decanoate Inj.	Dension Sicor Pharm.

1. REASSIGN FROM: MIC

DATE OF ORIGINAL ASSIGNMENT: _____

2. ASSIGN TO: Andrea High (A1H)

DATE OF REASSIGNMENT: _____

REASON FOR REASSIGNMENT: _____

/S/ 12/7/98

~~BRANCH SUPERVISOR~~ (SIGNATURE) DATE

CONCUR: ___ NOT CONCUR: ___

CHEMISTRY/BIOEQUIVALENCE
DIVISION DIRECTOR (SIGNATURE) DATE: _____

A COPY OF THIS FORM SHOULD BE PLACED IN EACH APPLICATION AND IN THE DIVISION FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-393

CORRESPONDENCE

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

January 22, 1999

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Haloperidol Decanoate Injection
50 mg Base/mL and 100 mg Base/mL
ANDA 75-393

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-393 for Haloperidol Decanoate Injection, 50 mg Base/mL and 100 mg Base/mL, which was submitted to the Agency on May 29, 1998. Reference is also made to our amendment dated January 12, 1999. Further reference is made to the telephone conversation today between Ms. Lilia Golson, Labeling Reviewer, OGD, and myself. Ms. Golson requested clarification with regard to the packaging of the 1 mL fill in the 2 mL vial.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide a description of the packaging configuration, plus a sample of the shelf pack carton as requested.

The shelf pack carton intended for packaging the 10-pack configuration of both the 50 mg/mL and 100 mg/mL products (1 mL fill) is an unprinted, fold and tuck style carton. The carton encloses the product and is designed to protect the product from light. The shelf pack label A (Part # Y29-105-101 [50 mg/mL] or Y29-102-801 [100 mg/mL]) is placed on the front panel of the carton. The shelf pack label B (Part # 1-7011-01 [50 mg/mL] or 1-7021-01 [100 mg/mL]) is placed on the back panel of the carton.

Please note, a sample of the shelf pack carton proposed for this product is currently under revision. The revision, being sought for the sample carton provided in this submission to prepare the carton intended for packaging the Haloperidol product, is that the preprinted Gensia Laboratories logo on the end panels will be eliminated.

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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PHARMACEUTICALS
A GensiaSicor Company

ember 16, 1998

Douglas Sporn
ce of Generic Drugs
ter for Drug Evaluation and Research
od and Drug Administration
ro Park North II, HFD-600
ention: Documentation and Control Room 150
00 Standish Place
ckville, MD 20855-2773

NDA ORIG AMENDMENT DR. Label
FA

RE: Haloperidol Decanote Injection
50 mg Base/mL and 100 mg Base/mL
ANDA 75-393

AMENDMENT

ear Mr. Sporn:

ference is made to Gensia Sicor's ANDA 75-393 for Haloperidol Decanoate Injection, 50 mg
se/mL and 100 mg Base/mL, which was submitted to the Agency on May 29, 1998. Reference is
o made to the Agency's facsimiles dated November 17 and December 7, 1998.

accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, w
reby amend our application to provide the additional information as requested.

e trust you will find the information in this amendment satisfactory for your review and approval.
ere are any questions concerning this amendment, please do not hesitate in contacting me at
49) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile a
49) 583-7351.

ncerely,

Elvia O. Gustafson
osalie A. Lowe
ssociate Director, Regulatory Affairs

RECEIVED
DEC 17 1998
GENERIC DRUGS

Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

December 16, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

OK Label
MAJOR AMENDMENT
FA

RE: Haloperidol Decanote Injection
50 mg Base/mL and 100 mg Base/mL
ANDA 75-393

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-393 for Haloperidol Decanoate Injection, 50 mg Base/mL and 100 mg Base/mL, which was submitted to the Agency on May 29, 1998. Reference is also made to the Agency's facsimiles dated November 17 and December 7, 1998.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information as requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

for Elvira O. Gustavson
Rosalie A. Lowe
Associate Director, Regulatory Affairs

RECEIVED
DEC 17 1998
GENERIC DRUGS

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

March 2, 1999

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

RE: Haloperidol Decanoate Injection
ANDA 75-393

AMENDMENT
RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-393 for Haloperidol Decanoate Injection, 50 mg Base/mL and 100 mg Base/mL, which was submitted to the Agency on May 29, 1998. Reference is also made to the Agency's facsimile dated February 16, 1999.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\RGV\Hal75393\AMENDS\Amend4.doc

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

RECEIVED
MAR 0 3 1999
GENERIC DRUGS

Microbiology Deficiency:

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

April 20, 1999

NDA ORIG AMENDMENT
N/FA

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Haloperidol Decanoate Injection
ANDA 75-393

TELEPHONE AMENDMENT

RECEIVED
APR 21 1999

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-393 for Haloperidol Decanoate Injection, 50 mg Base/mL and 100 mg Base/mL, which was submitted to the Agency on May 29, 1998. Reference is also made to the tele-conference with the Chemistry Reviewer at the Agency dated April 8, 1999.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional information requested.

Per our conversation, we have revised the impurity specifications to monitor the specific impurity at RRT ≈0.8. Below is a summary table of our proposed impurity specifications:

Test	Release Specification	Shelf-Life Specification
Impurity at RRT ≈0.8, %	NMT	NMT
Other Single Largest Impurity, %	NMT	NMT
Total Impurities, %	NMT	NMT

Based upon 12 months of stability data for our product and data on various lots of innovator product, we propose a stability specification of NMT for the impurity at RRT ≈0.8, with a release specification of NMT . In addition, as a result of our impurity analyses for our product and the innovator's product, we had increased the specification for Total Impurities to NMT . This increase in the Total Impurity specification is necessary to allow for degradation attributed to the impurity at RRT ≈0.8.

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The table below summarizes the data we reference in support of our proposed specifications:

Test	50 mg/mL			
	1 mL fill		5 mL fill	
	GSPI 12-month	Innovator Exp. 9/00	GSPI 12-month	Innovator Two Lots Exp. 10/99
Impurity at RRT ~0.8, %				
Other Single Largest Impurity, %				
Total Impurities, %				
Test	**100 mg/mL**			
	1 mL fill		5 mL fill	
	GSPI 12-month	Innovator Exp. 6/00	GSPI 12-month	Innovator One Lot Exp. 10/99* Three Lots Exp. 5/99
Impurity at RRT ~0.8, %				
Other Single Largest Impurity, %				
Total Impurities, %				

The observed trend for our products are confirmed as being appropriate as demonstrated by the comparative impurity levels observed for the innovator products.

In addition to discussing the impurity specifications, you requested clarification regarding the oxygen headspace monitoring of the exhibit lots during stability. Specifically, you requested clarification as to why we have not listed a specification for oxygen headspace in our stability data tables. We contend that this product is similar to Fluphenazine Decanoate Injection, an approved Gensia Sicor product, which is also formulated in an . Due to our experience with this type of formulation, we expect the oxygen headspace to decrease over time as we have seen with Fluphenazine Decanoate Injection.

To confirm our expectations, we have monitored the oxygen headspace of our proposed products during stability and collected the data as "information only." As demonstrated thus far, the oxygen headspace has decreased as expected. We intend to continue monitoring oxygen headspace over the remainder of the stability study for the exhibit lots. However, as noted in our original application and the commercial stability protocol, we intend to monitor oxygen headspace only at release for the commercial products and do not intend to monitor oxygen headspace as part of our commercial stability program for these products.

The current stability data sheets are enclosed and include results of the all stability studies completed to date for the proposed products. Additionally, as requested these data sheets have been revised to include our specification for oxygen headspace.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen, Regulatory Affairs Project Specialist, at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

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cc: Ms. Elaine Messa
District Director
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