CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-918

Name: Fluphenazine Decanoate Injection USP, 25 mg/mL

Sponsor: Apotex Corp.

Approval Date: August 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter(s)	
Approved Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	
Microbiology Review(s)	X
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

APPROVAL LETTER

ANDA 75-918

AUG 17 2001

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 June 30, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluphenazine Decanoate Injection USP, 25 mg/mL.

Reference is also made to your amendments dated February 10, June 12, June 21, and July 31, 2001.

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 Fluphenazine Decanoate Injection USP, 25 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Prolixin Decanoate Injection, 25 mg/mL of Apothecon Inc.).

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 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,

Robert Lewest/for 8/17/2001

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-918
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205

Endorsements:
HFD-623/J.Franolic/ John J. Franolic 8/14/01
HFD-623/D.Gill/ DSGill 8-14-01
HFD-617/R.Yu/ Ryu 8-16-01
HFD-600/N.Nath/ NN2 8/14/01
HFD-640/A.High/ AH 8/15/01
HFD-613/D.Catterson/ Debra M. Catterson 8/15/01
HFD-613/J.Grace/ J Grace 8/15/2001

V:\FIRMSAM\APOTEX\LTRS&REV\75918.ap.doc

F/T by: DJ 8/14/01

APPROVAL

Robert L. West 8/17/2001

Faxed 8/16/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

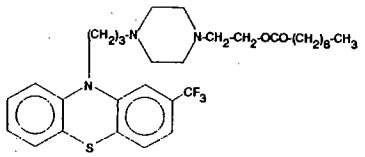
APPROVED LABELING

FLUPHENAZINE DECANOATE INJECTION, USP
25 mg/mL
Rx Only

ENLARGED TO 110% BY FDI STAFF

DESCRIPTION

Fluphenazine decanoate is the decanoate ester of a trifluoromethyl phenothiazine derivative. Fluphenazine Decanoate is 2-4-[3-(2-trifluoromethylphenothiazin-10-yl)-propyl]-piperazin-1-yl]ethyl decanoate. It is a highly potent behavior modifier with a markedly extended duration of effect. Fluphenazine Decanoate Injection is a sterile solution available for intramuscular or subcutaneous administration, providing 25 mg fluphenazine decanoate per mL in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as a preservative. Fluphenazine decanoate has the following structural formula:



$C_{32}H_{44}F_3N_3O_2S$ 591.8

CLINICAL PHARMACOLOGY

The basic effects of fluphenazine decanoate appear to be no different from those of fluphenazine hydrochloride, with the exception of duration of action. The esterification of fluphenazine markedly prolongs the drug's duration of effect without unduly attenuating its beneficial action.

Fluphenazine decanoate has activity at all levels of the central nervous system as well as on multiple organ systems. The mechanism whereby its therapeutic action is exerted is unknown.

Fluphenazine differs from other phenothiazine derivatives in several respects: it is more potent on a milligram basis, it has less potentiating effect on central nervous system depressants and anesthetics than do some of the phenothiazines and appears to be less sedating, and it is less likely than some of the older phenothiazines to produce hypotension (nevertheless, appropriate cautions should be observed – see sections on **PRECAUTIONS** and **ADVERSE REACTIONS**).

INDICATIONS AND USAGE

Fluphenazine Decanoate Injection is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral neuroleptic therapy (e.g., chronic schizophrenics).

Fluphenazine Decanoate Injection has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

Phenothiazines are contraindicated in patients with suspected or established subcortical brain damage.

Phenothiazine compounds should not be used in patients receiving large doses of hypnotics.

Fluphenazine Decanoate Injection is contraindicated in comatose or severely depressed states.

The presence of blood dyscrasia or liver damage precludes the use of fluphenazine decanoate.

Fluphenazine Decanoate Injection is not intended for use in pediatric patients under 12 years of age.

Fluphenazine Decanoate Injection is contraindicated in patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur.

WARNINGS

Tardive Dyskinesia:
Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (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 neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic 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 neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic 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 neuroleptics, 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 the sections on **PRECAUTIONS, Information for Patients** and **ADVERSE REACTIONS, Tardive Dyskinesia**).

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 and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

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.

The use of this drug may impair the mental and physical abilities required for driving a car or operating heavy machinery.

Physicians should be alert to the possibility that severe adverse reactions may occur which require immediate medical attention.

Potentiation of the effects of alcohol may occur with the use of this drug.

Since there is no adequate experience in pediatric patients who have received this drug, safety and efficacy in pediatric patients have not been established.

Usage in Pregnancy:
The safety for the use of this drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential benefits when administering this drug to pregnant patients.

PRECAUTIONS

General:
Because of the possibility of cross-sensitivity, fluphenazine decanoate should be used cautiously in patients who have developed cholestatic jaundice, dermatoses, or other allergic reactions to phenothiazine derivatives.

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or central nervous system depressants may be necessary.

The effects of atropine may be potentiated in some patients receiving fluphenazine because of added anticholinergic effects.

Fluphenazine decanoate should be used cautiously in patients exposed to extreme heat or phosphorus insecticides.

The preparation should be used with caution in patients with a history of convulsive disorders, since grand mal convulsions have been known to occur.

Use with caution in patients with special medical disorders such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma.

The possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia should be remembered when patients are on prolonged therapy.

Outside state hospitals or other psychiatric institutions, fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs, particularly phenothiazine derivatives. Furthermore, facilities should be available for periodic checking of hepatic function, renal function, and the blood picture. Renal function of patients on long-term therapy should be monitored; if BUN (blood urea nitrogen) becomes abnormal, treatment should be discontinued.

As with any phenothiazine, the physician should be alert to the possible development of "silent pneumonias" in patients under treatment with fluphenazine decanoate.

Neuroleptic 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 neuroleptic 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.

Information for Patients:
Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or

their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

ADVERSE REACTIONS

Central Nervous System:
The side effects most frequently reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. Most often these extrapyramidal symptoms are reversible; however, they may be persistent (see below). The frequency of such reactions is related in part to chemical structure: one can expect a higher incidence with fluphenazine decanoate than with less potent piperazine derivatives or with straight-chain phenothiazines such as chlorpromazine. With any given phenothiazine derivative, the incidence and severity of such reactions depend more on individual patient sensitivity than on other factors, but dosage level and patient age are also determinants.

Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions can usually be controlled by administration of antiparkinsonian drugs such as Benztropine Mesylate or Intravenous Caffeine and Sodium Benzoate Injection, and by subsequent reduction in dosage.

Tardive Dyskinesia:
See **WARNINGS**. The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, since neuroleptic drugs may mask the signs of the syndrome.

Other CNS Effects:
Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see **WARNINGS, Neuroleptic Malignant Syndrome**); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induction of a catatonic-like state has been known to occur with dosages of fluphenazine far in excess of the recommended amounts. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams.

Autonomic Nervous System:
Hypertension and fluctuations in blood pressure have been reported with fluphenazine.

Hypotension has rarely presented a problem with fluphenazine. However, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. If severe hypotension should occur, supportive measures including the use of intravenous vasopressor drugs should be instituted immediately. Levarterenol Bitartrate Injection is the most suitable drug for this purpose; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.

Autonomic reactions including nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Autonomic effects can usually be controlled by reducing or temporarily discontinuing dosage.

In some patients, phenothiazine derivatives have caused blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion.

Metabolic and Endocrine:
Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have all been known to occur in some patients on phenothiazine therapy.

Allergic Reactions:
Skin disorders such as itching, erythema, urticaria, seborrhea, photosensitivity, eczema and even exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

Hematologic:
Routine blood counts are advisable during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic:
Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests, has been reported in patients receiving the enanthate ester of fluphenazine (a closely related compound) who have had no clinical evidence of liver damage.

Others:
Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.

Although this is not a general feature of fluphenazine, potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

The following adverse reactions have also occurred with phenothiazine derivatives: systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use—skin pigmentation, and lenticular and corneal opacities.

Injections of fluphenazine decanoate are extremely well tolerated, local tissue reactions occurring only rarely.

DOSAGE AND ADMINISTRATION

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

Fluphenazine Decanoate Injection may be given intramuscularly or subcutaneously. A dry syringe and needle of at least 21 gauge should be used. Use of a wet needle or syringe may cause the solution to become cloudy.

To begin therapy with Fluphenazine Decanoate Injection the following regimens are suggested:

For most patients, a dose of 12.5 to 25 mg (0.5 to 1 mL) may be given to initiate therapy. The onset of action generally appears between 24 and 72 hours after injection and the effects of the drug on psychotic symptoms becomes significant within 48 to 96 hours. Subsequent injections and the dosage interval are determined in accordance with the patient's response. When administered as maintenance therapy, a single injection may be effective in controlling schizophrenic symptoms up to four weeks or longer. The response to a single dose has been found to last as long as six weeks in a few patients on maintenance therapy.

It may be advisable that patients who have no history of taking phenothiazines should be treated initially with a shorter-acting form of fluphenazine before administering the decanoate to determine the patient's response to fluphenazine and to establish appropriate dosage. For psychotic patients who have been stabilized on a fixed daily dosage of Fluphenazine Hydrochloride Tablets, Fluphenazine Hydrochloride Elixir, or Fluphenazine Hydrochloride Oral Solution, conversion of therapy from these short-acting oral forms to the long-acting Fluphenazine Decanoate Injection may be indicated.

Appropriate dosage of Fluphenazine Decanoate Injection should be individualized for each patient and responses carefully monitored. No precise formula can be given to convert to use of Fluphenazine Decanoate Injection; however, a controlled multicentered study*, in patients receiving oral doses from 5 to 60 mg fluphenazine hydrochloride daily, showed that 20 mg fluphenazine hydrochloride daily was equivalent to 25 mg (1 mL) Fluphenazine Decanoate Injection every three weeks. This represents an approximate conversion ratio of 0.5 mL (12.5 mg) of decanoate every three weeks for every 10 mg of fluphenazine hydrochloride daily.

Once conversion to Fluphenazine Decanoate Injection is made, careful clinical monitoring of the patient and appropriate dosage adjustment should be made at the time of each injection.

Severely agitated patients may be treated initially with a rapid-acting phenothiazine compound such as Fluphenazine Hydrochloride Injection—see package insert accompanying that product for complete information. When acute symptoms have subsided, 25 mg (1 mL) of Fluphenazine Decanoate Injection may be administered; subsequent dosage is adjusted as necessary.

"Poor risk" patients (those with known hypersensitivity to phenothiazines, or with disorders that predispose to undue reactions): Therapy may be initiated cautiously with oral or parenteral fluphenazine hydrochloride (see package inserts accompanying these products for complete information). When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of Fluphenazine Decanoate Injection may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient.

The optimal amount of the drug and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug.

Dosage should not exceed 100 mg. If doses greater than 50 mg are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5 mg.

HOW SUPPLIED

Fluphenazine Decanoate Injection, USP 25 mg/mL is available as follows:

5 mL Multiple Dose Vial

At the time of manufacture, the air in the vials is replaced by nitrogen.

Each vial is individually cartoned.

Storage:
Store at controlled room temperature 15° to 30°C (59° to 86°F). Avoid freezing and excessive heat.

PROTECT FROM LIGHT.

*The Initiation of Long-Term Pharmacotherapy in Schizophrenia: Dosage and Side Effect Comparisons Between Oral and Depot Fluphenazine; N.R. Schooler; Pharmakopsych. 9:159-169, 1976.

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

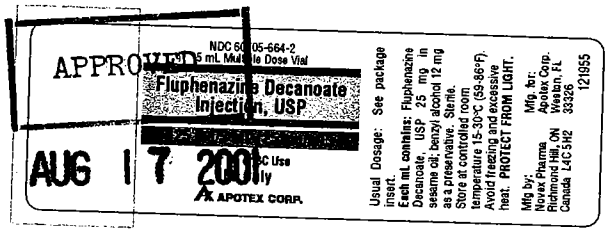
Mfg for:
Apotex Corp.
Weston FL, 33326

121957

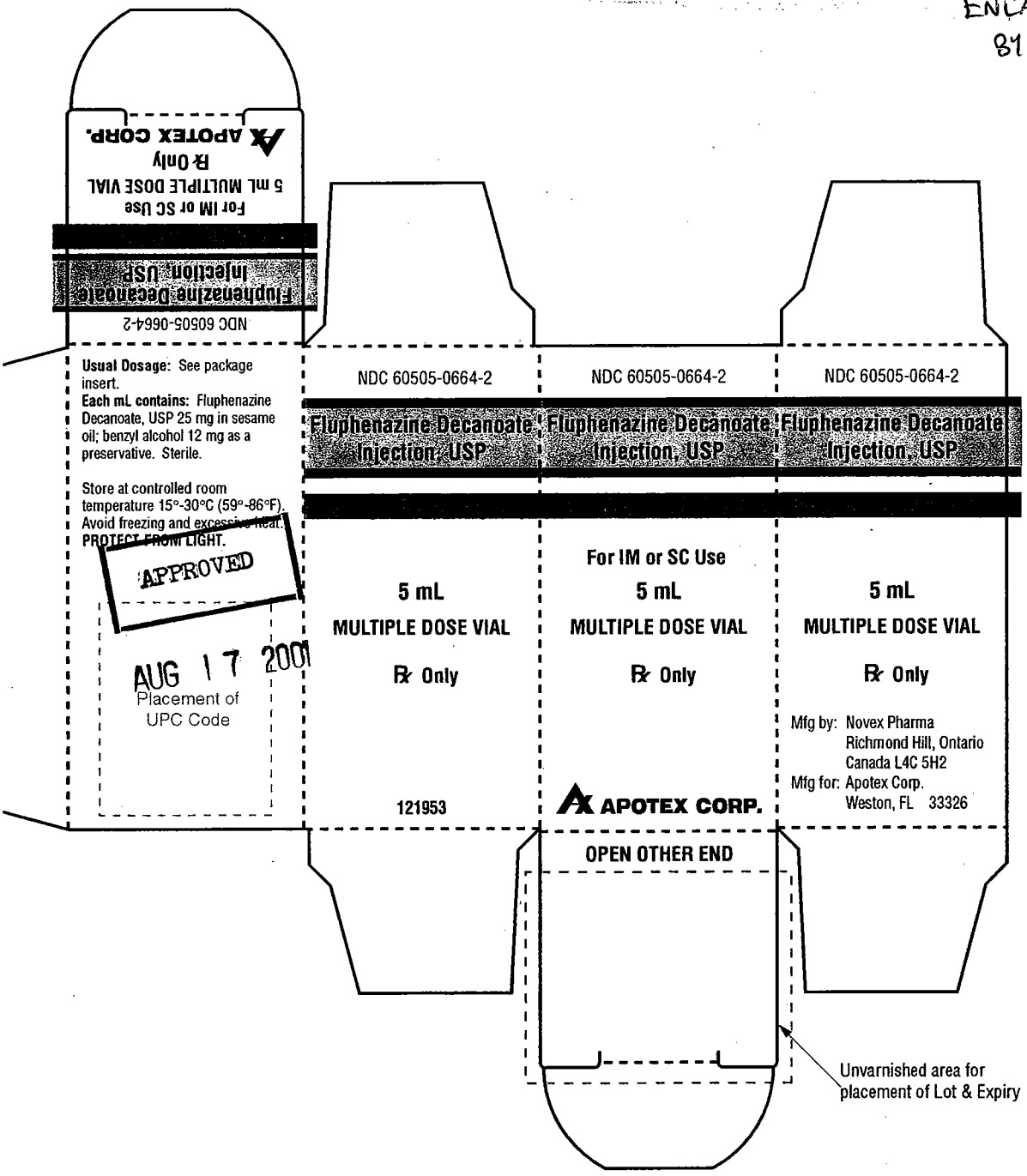
June 2001

Original

ENLARGED TO 120%
BY FOIA STAFF



ENLARGED TO 110%
BY FDI STAFF



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

LABELING REVIEW(S)

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

ANDA Number: 75-918

Date of Submission: June 30, 2000 (Original draft labeling)

Applicant's Name: Apotex Corporation

Established Name: Fluphenazine Decanoate Injection USP, 25 mg/mL

Labeling Deficiencies:

1. **CONTAINER** (5 mL Multiple Dose vial):

   Satisfactory in draft.

2. **CARTON** (1 x 5 mL Multiple Dose vial):

   Satisfactory in draft.

3. **INSERT**

   Please refer to pages "62, 63, 64, 65, 68, 72, 73, and 74" of the attached mocked-up copy of your insert labeling for all of the requested labeling revisions.

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.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of firm's mocked-up labeling.

Mocked-up draft labeling was removed from this document.

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 24	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	
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 (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)? The product contains benzyl alcohol as a preservative, but the drug is not intended for use in the neonate population.		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.		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.**		X	

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for the reference listed drug, Prolixin® Decanoate Injection, by Apothecon (NDA 16-727/S-046; permitted without approval September 28,1987).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 16-727

No.	Expiration	Use Code	Use	File
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A

Exclusivity Data– NDA 16-727

Code	Reference	Expiration
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A

The firm's statements are correct. [Vol. A1.1 pg. 007.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Novex Pharma
380 Elgin Mills Road, East
Richmond Hill, Ontario
Canada L4C 5H2 [Vol. A1.1 pg. 235.]

4. CONTAINER/CLOSURE

Vial: 5 ml, 13 mm, Type I USP Clear Glass Serum Vial
Closure: 13 mm Gray Elastomeric Serum Stopper, [redacted]
Seal: 13 mm Aluminum Crimp Cap with Blue [redacted] plastic cover embossed with "Flip Cap" on opposite sides of each other.
[Vol. A1.1 p. 276; and Vol. A1.2 pgs. 465, 506, 512, 559, & 572.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the components and composition statement.
[Vol. A1.1 page 126]

6. PACKAGING CONFIGURATIONS

RLD: "Unimatic" single dose syringes
Unit cartons of 1 X 5 ml multiple dose vial.
ANDA:
Unit cartons of 1 X 5 ml multiple dose vial.
[Vol. A1.1 pg. 37]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Preserve in single-dose or in multiple-dose containers, of Type I glass, protected from light.
RLD: Store at room temperature; avoid freezing and excessive heat. Protect from light.
ANDA: Store at controlled room temperature (15°-30°C, 59°-86°F). Avoid freezing and excessive heat. Protect from light.
[Vol. A1.1, pg. 37]

8. BIOAVAILABILITY/BIOEQUIVALENCE:

On August 31, 2000, the Division of Bioequivalence granted the firm's request for a waiver of *in vivo* bioequivalence study requirements.

9. MICROBIOLOGY

The microbiologist's review of January 10, 2001 did not recommend the application for approval, due to a lack of sterility assurance.

Date of Review: 3/27/01 Date of Submission: 6/30/00

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 3/30/01

Team Leader: John Grace Date:

4/3/2001

---

cc:

ANDA: 75-918
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\apotex\ltrs&rev\75918NA1.L.doc
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 75-918

Date of Submission: June 21, 2001 (Amendment - FPL)

Applicant's Name: Apotex Corporation

Established Name: Fluphenazine Decanoate Injection USP, 25 mg/mL

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 (5 mL Multiple Dose Vial):
Satisfactory as of the June 21, 2001 submission. [Vol. 2.1, "Section III", Manufac. Code: 121955]

CARTON Labels (1 x 5 mL Multiple Dose Vial):
Satisfactory as of the June 21, 2001 submission. [Vol. 2.1, "Section III", Manufac. Code: 121953]

Professional Package Insert Labeling:
Satisfactory as of the June 21, 2001 submission. [Vol. 2.1, "Section III"; Revised June 2001; Manufacturer's Code: 121957]

Revisions needed post-approval: None.

Patent Data – NDA 16-727

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 16-727

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prolixin® Decanoate Injection

NDA Number: 16-727

NDA Drug Name: Prolixin® (fluphenazine) Decanoate Injection

NDA Firm: Apothecon

Date of Approval of NDA Insert and Supplement : September 28, 1987/S-045 & S-046 (permitted without approval)

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 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 24**	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	
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 (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)? **The product contains benzyl alcohol as a preservative, but the drug is not intended for use in the neonate population.**		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.		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.**		X	

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for the reference listed drug, Prolixin® Decanoate Injection, by Apothecon (NDA 16-727/S-045 & S-046; permitted without approval September 28,1987).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 16-727

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 16-727

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 007.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Novex Pharma
380 Elgin Mills Road, East
Richmond Hill, Ontario
Canada L4C 5H2 [Vol. A1.1 pg. 235.]

4. CONTAINER/CLOSURE

Vial: 5 ml, 13 mm, Type I USP Clear Glass Serum Vial
Closure: 13 mm Gray Elastomeric Serum Stopper, ———
Seal: 13 mm Aluminum Crimp Cap with Blue ———— plastic cover embossed with "Flip Cap" on opposite sides of each other.
[Vol. A1.1 p. 276; and Vol. A1.2 pgs. 465, 506, 512, 559, & 572.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the components and composition statement.
[Vol. A1.1 page 126]

6. PACKAGING CONFIGURATIONS

RLD: "Unimatic" single dose syringes
Unit cartons of 1 X 5 ml multiple dose vial.
ANDA:
Unit cartons of 1 X 5 ml multiple dose vial.
[Vol. A1.1 pg. 37]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Preserve in single-dose or in multiple-dose containers, of Type I glass, protected from light.
RLD: Store at room temperature; avoid freezing and excessive heat. Protect from light.
ANDA: Store at controlled room temperature (15°-30°C, 59°-86°F). Avoid freezing and excessive heat.

Protect from light.
[Vol. A1.1, pg. 37]

8. BIOAVAILABILITY/BIOEQUIVALENCE:

   On August 31, 2000, the Division of Bioequivalence granted the firm's request for a waiver of *in vivo* bioequivalence study requirements.

9. MICROBIOLOGY

   Acceptable as of April 9, 2001

Date of Review: 6/27/01 Date of Submission: 6/21/01

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 6/29/01

Team Leader: John Grace Date:

Gilda N Dalsan for 6/29/01

---

cc:

ANDA: 75-918
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\apotex\ltrs&rev\75918APL.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** No. 1

2. **ANDA #** 75-918 [**Fluphenazine Decanoate Injection, USP 25 mg/mL**]

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

4. **LEGAL BASIS OF SUBMISSION:**
Reference Listed Drug: **Prolixin® Decanoate Injection 25 mg/mL**
Manufacturer: Apothecon (NDA # 16-727)

The applicant has certified that in their opinion and to the best of their knowledge, all patents relates to Prolixin® Decanoate Injection 25 mg/mL, held by Apothecon, have expired, and there is no marketing exclusivity currently in effect.

Since 1996, OGD has approved the following ANDAs for Fluphenazine Decanoate Injection, USP 25 mg/mL:

ANDA Number	Applicant	Review Chemist	Date of Approval
74-531	Bedford	N. Nashed	08/30/96
74-795	Gesia	A. Mueller	09/10/96
74-966	King Pharm	M. Shaikh	04/16/98

(Note: ANDA 71-413 was approved on 07/14/87--First Generic Approval)

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Fluphenazine Decanoate Injection, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Apotex:
06/30/00 Original submission (receive on 07/03/00)

FDA:
07/03/00 Date Acceptable for filing
08/14/00 Date of acknowledgment letter

10. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
NDA: 16-727
See Item 37 for DMF list and comments.

13. **DOSAGE FORM**: Injection

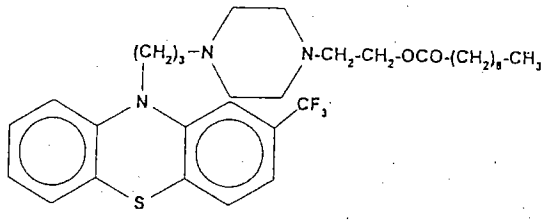
14. **STRENGTH**: 25 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**:
Molecular formula: $C_{32}H_{44}F_3N_3O_2S$

Chemical name:
2-[4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]-1-piperazinyl]ethyl decanoate

Molecular weight: 591.8

Structural formula:



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

17. **COMMENTS**:
The drug substance and drug product are listed in the USP 24. Method validation by FDA lab is not required. Type II DMF for the [redacted] is deficient. There are a few CMC deficiencies. The estimated review time for the response to these deficiencies is less than one hour for an average review chemist.

There is no deficiency in bioequivalence. The sterility assurance and labeling portions of the ANDA are pending. Acceptable EER has not been received.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (MINOR amendment)

19. **REVIEWER**: Shing H. Liu, Ph.D. **DATE COMPLETED**: 11/24/2000
Revised 12/06/00

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-918 **APPLICANT:** Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection, USP 25 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

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

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

1. Please be advised that the 27-page Study Protocol SP-AN-750-02.00 appeared in two sections of the ANDA (pp. 626-648, and pp. 730-736). Moreover, Appendix 2 of the Analytical Report AR-750-001-00 is not found after Appendix 1 (it appeared on page 737).

2. Please be advised that the use of in-house analytical methods for testing the drug substance and drug product does not relieve you from meeting the compendial standards. In the event of a dispute, the official USP methods will prevail.

3. The sterility assurance and labeling portion of the ANDA are under review. Deficiencies, if any, will be conveyed to you under separate cover(s).

4. Please submit all available room temperature stability data.

5. Please contact the District Office concerning your vendor qualification protocol for drug substance (p. 170).

Sincerely yours,

12/13/96

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

cc: ANDA 75-918
Field Copy
Division File

Endorsements:

HFD-623/S.Liu, Ph.D./11-24-00/12-06-00 S.H. Liu 12/06/00
HFD-623/D.Gill, Ph.D./12-01-00/ DSGill 12-7-00
HFD-619/R.Yu, Pharm. D./ RYu 12-7-00

V:\firmsam\apotex\ltrs&rev\75918cr1.fluphenazine.apotex.doc

F/T by: shl 12-06-00

Not Approvable (MINOR AMENDMENT)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW #** **No. 2**

2. **ANDA #** 75-918 **[Fluphenazine Decanoate Injection, USP 25 mg/mL]**

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 Drug: **Prolixin® Decanoate Injection 25 mg/mL**
Manufacturer: Apothecon (NDA # 16-727)

The applicant has certified that in their opinion and to the best of their knowledge, all patents relates to Prolixin® Decanoate Injection 25 mg/mL, held by Apothecon, have expired, and there is no marketing exclusivity currently in effect.

Since 1996, OGD has approved the following ANDAs for Fluphenazine Decanoate Injection, USP 25 mg/mL:

ANDA Number	Applicant	Review Chemist	Date of Approval
74-531	Bedford	N. Nashed	08/30/96
74-795	Gesia	A. Mueller	09/10/96
74-966	King Pharm	M. Shaikh	04/16/98

(Note: ANDA 71-413 was approved on 07/14/87--First Generic Approval)

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Fluphenazine Decanoate Injection, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Apotex:

06/30/00	Original submission (receive on 07/03/00)
02/21/01	Minor Amendment

FDA:

07/03/00	Date Acceptable for filing
08/14/00	Date of acknowledgment letter
12/14/00	Deficiency (Minor) Letter

10. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

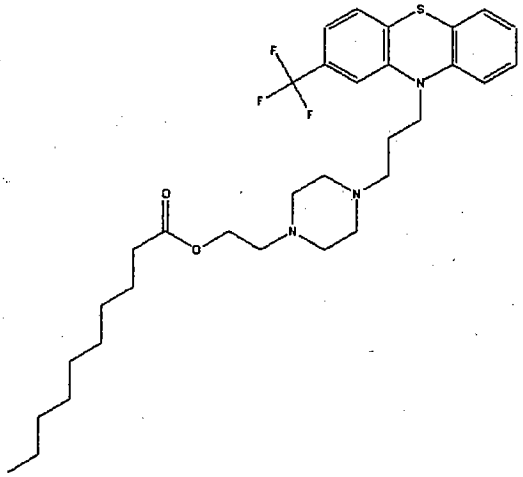
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
NDA: 16-727. See Item 37 for DMF list and comments.

13. **DOSAGE FORM**: Injection

14. **STRENGTH**: 25 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**:
Molecular formula: $C_{32}H_{44}F_3N_3O_2S$
Chemical name: 2-4-[3-(2-(Trifluoromethylphenothiazin-10-yl)-propyl]ethyl decanoate. Molecular weight: 591.8
Structural formula:



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

17. **COMMENTS**:
The applicant submitted an amendment (dated 2/21/01) to address the CMC deficiencies cited in the Agency's 12/14/00 letter. The Type II DMF # ——for the ———————— is not adequate. The drug substance and drug product are listed in the USP 24. Method validation by FDA lab is not required.

There is no deficiency in bioequivalence. The microbiology review recommends approval for lack of sterility assurance. The labeling portion of the ANDA is pending. Acceptable EER received.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (MINOR amendment)

19. **REVIEWER**: John D. Franolic, Ph.D. **DATE COMPLETED**: 03/29/2001

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-918 **APPLICANT:** Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection USP, 25 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

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

1. Please submit all available room temperature stability data.

2. Please contact the District Office concerning your vendor qualification protocol for drug substance (p. 170).

Sincerely yours,

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

cc: ANDA 75-918
Field Copy
Division File

Endorsements:

HFD-623/John D. Franolic, Ph.D./03/29/01 John D. Franolic 3/29/01
HFD-623/Upinder Atwal for D.Gill, Ph.D./04/02/01
HFD-619/R.Yu, Pharm. D./04/03/01

V:\firmsam\apotex\ltrs&rev\75918cr2.Fluphenazine.apotex.doc

F/T by: gp/04/04/01

Not Approvable (MINOR AMENDMENT)

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW #** No. 3

2. **ANDA #** 75-918 [**Fluphenazine Decanoate Injection, USP 25 mg/mL**]

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 Drug: **Prolixin® Decanoate Injection 25 mg/mL**
Manufacturer: Apothecon (NDA # 16-727)

The applicant has certified that in their opinion and to the best of their knowledge, all patents relates to Prolixin® Decanoate Injection 25 mg/mL, held by Apothecon, have expired, and there is no marketing exclusivity currently in effect.

Since 1996, OGD has approved the following ANDAs for Fluphenazine Decanoate Injection, USP 25 mg/mL:

ANDA Number	Applicant	Review Chemist	Date of Approval
74-531	Bedford	N. Nashed	08/30/96
74-795	Gesia	A. Mueller	09/10/96
74-966	King Pharm	M. Shaikh	04/16/98

(Note: ANDA 71-413 was approved on 07/14/87--First Generic Approval)

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Fluphenazine Decanoate Injection, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Apotex:

06/30/00	Original submission (receive on 07/03/00)
02/10/01	Microbiology Amendment (Response to 1/17/01 letter)
02/21/01	Minor Amendment (Response to NA Minor 12/14/00)
06/12/01	Minor Amendment (Response to NA Minor 4/9/01)

FDA:

07/03/00	Date Acceptable for filing
08/14/00	Date of acknowledgment letter
08/31/00	Bioequivalence acceptable
12/14/00	CMC Deficiency (NA Minor) Letter

01/17/01	Microbiology Deficiency Letter
04/03/01	Labeling Deficiency Letter
04/09/01	CMC Deficiency (NA MINOR) Letter

10. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

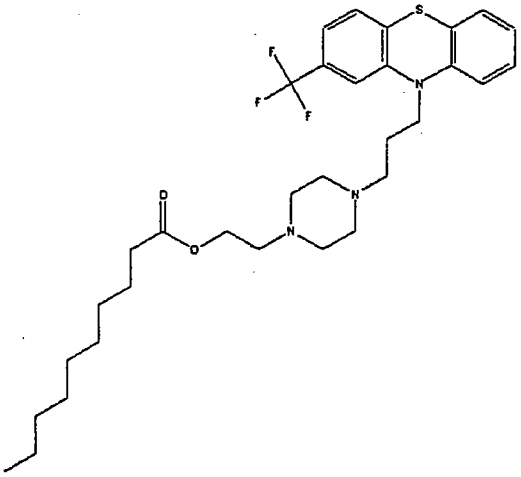
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
NDA: 16-727. See Item 37 for DMF list and comments.

13. **DOSAGE FORM**: Injection

14. **STRENGTH**: 25 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**:
Molecular formula: $C_{32}H_{44}F_3N_3O_2S$
Chemical name: 2-4-[3-(2-(Trifluoromethylphenothiazin-10-yl)-propyl]ethyl decanoate. Molecular weight: 591.8
Structural formula:



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

17. **COMMENTS**:
DMF #——— for the ——————— has been found adequate this review cycle. The drug substance and drug product are listed in the USP 24. Method validation by FDA lab is not required.

Bioequivalency was found acceptable 8/31/00. The microbiology review recommends approval for sterility assurance 3/2/01. The labeling was approved 6/29/01. Acceptable EER received 11/30/00.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Not Approvable

19. **REVIEWER**: John D. Franolic, Ph.D. **DATE COMPLETED**: 06/22/2001
Revised 7/09/01

BACKGROUND INFORMATION:
In the Minor Amendment dated 6/12/01, the firm submitted responses to the deficiencies cited in the NA (MINOR) letter dated 4/9/01. The applicant's responses to the deficiencies along with additional

Redacted 9 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #3

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-918 APPLICANT: Apotex Corporation

DRUG PRODUCT: Fluphenazine Decanoate Injection USP, 25 mg/mL

The deficiencies presented below represent Telephone deficiencies:

1. [redacted]

2.

3.

Sincerely yours,

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

cc: ANDA 75-918
Field Copy
Division File

APPEARS THIS WAY ON ORIGINAL

Endorsements:

HFD-623/John D. Franolic, Ph.D./07/09/01 John D. Franolic 7/9/01
HFD-623/D.Gill, Ph.D./07/09/01 DSGill 7-17-01
HFD-619/PBeersBlock for R.Yu, Pharm. D./07/11/01 PBeersBlock for RY 7/13/01

V:\firmsam\apotex\ltrs&rev\75918cr3.Fluphenazine.apotex.doc

F/T by: gp/07/11/01

Not Approvable (~~FAX~~) Telephone gp 7/23/01

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW # Addendum to Review #3**

2. **ANDA #** 75-918 [**Fluphenazine Decanoate Injection, USP 25 mg/mL**]

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 Drug: **Prolixin® Decanoate Injection 25 mg/mL**
Manufacturer: Apothecon (NDA # 16-727)

The applicant has certified that in their opinion and to the best of their knowledge, all patents relates to Prolixin® Decanoate Injection 25 mg/mL, held by Apothecon, have expired, and there is no marketing exclusivity currently in effect.

Since 1996, OGD has approved the following ANDAs for Fluphenazine Decanoate Injection, USP 25 mg/mL:

ANDA Number	Applicant	Review Chemist	Date of Approval
74-531	Bedford	N. Nashed	08/30/96
74-795	Gesia	A. Mueller	09/10/96
74-966	King Pharm	M. Shaikh	04/16/98

(Note: ANDA 71-413 was approved on 07/14/87--First Generic Approval)

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Fluphenazine Decanoate Injection, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Apotex:

06/30/00	Original submission (receive on 07/03/00)
02/10/01	Microbiology Amendment (Response to 1/17/01 letter)
02/21/01	Minor Amendment (Response to NA Minor 12/14/00)
06/12/01	Minor Amendment (Response to NA Minor 4/9/01)
07/23/01	Fax (questions regarding 7/18/01 Telephone deficiency)
07/31/01	Telephone Amendment

FDA:

07/03/00	Date Acceptable for filing
08/14/00	Date of acknowledgment letter
08/31/00	Bioequivalence acceptable
12/14/00	CMC Deficiency (NA Minor) Letter
01/17/01	Microbiology Deficiency Letter
04/03/01	Labeling Deficiency Letter

04/09/01 CMC Deficiency (NA MINOR) Letter
07/18/01 Telephone Deficiency

10. **PHARMACOLOGICAL CATEGORY**: Antipsychotic

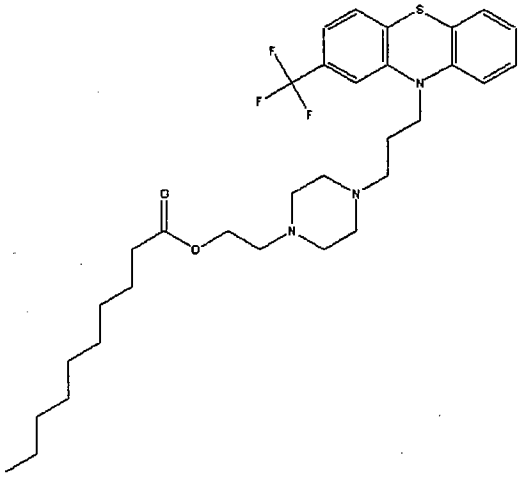
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
NDA: 16-727. See Item 37 for DMF list and comments.

13. **DOSAGE FORM**: Injection

14. **STRENGTH**: 25 mg/mL

15. **CHEMICAL NAME AND STRUCTURE:**
Molecular formula: $C_{32}H_{44}F_3N_3O_2S$
Chemical name: 2-4-[3-(2-(Trifluoromethylphenothiazin-10-yl)-propyl]ethyl decanoate. Molecular weight: 591.8
Structural formula:



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

17. **COMMENTS**:
DMF #[redacted] for the [redacted] was found adequate last review cycle. The drug substance and drug product are listed in the USP 24. Method validation by FDA lab is not required.

Bioequivalency was found acceptable 8/31/00. The microbiology review recommends approval for sterility assurance 3/2/01. The labeling was approved 6/29/01. Acceptable EER received 11/30/00.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Approvable

19. **REVIEWER**: John D. Franolic, Ph.D. **DATE COMPLETED**: 08/06/2001

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW - ADDENDUM TO REVIEW #3

cc: ANDA 75-918
Field Copy
Division File

Endorsements:

HFD-623/John D. Franolic, Ph.D./08-06-01 John D. Franolic 8/14/01
HFD-623/D.Gill, Ph.D./8/6/01 DSGill 8-14-01
HFD-619/R.Yu, Pharm. D./8/14/01 RY 8-16-01

V:\firmsam\apotex\ltrs&rev\75918cr4.Fluphenazine.apotex.doc
F/T by: DJ 8/14/01

Approvable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

BIOEQUIVALENCE REVIEW(S)

AUG 3 1 2000

Fluphenazine Decanoate Injection USP
25 mg/mL
ANDA # 75-918
Reviewer: Hoainhon Nguyen
W # 75918w.600

Apotex Corp.
Vernon Hills, IL
Submission Date:
June 30, 2000

Review of a Waiver Request

The firm has requested a waiver from *in vivo* bioavailability requirements for its Fluphenazine Decanoate Injection USP, 25 mg/mL, in accordance with 21 CFR 320.22 (b) (1).

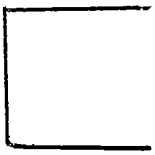
Comments:

1. The test product is a parenteral solution intended solely for administration by injection.

2. The formulation of the test product is identical to that of the currently approved Prolixin® Decanoate Injection, 25 mg/mL, manufactured by Apothecon (Squibb), as shown below:

Ingredients	Test Formulation (per mL)	Prolixin's Formulation (per mL)
Fluphenazine Decanoate	25 mg	25 mg
Benzyl Alcohol, NF	12 mg	12 mg
Sesame Oil*	q.s.	q.s.

*NOTE: (Not to be released under FOI) Apotex uses a ——— Sesame Oil. Another approved generic product, King Pharmaceuticals' Fluphenazine Decanoate Injection, 25 mg/mL, ANDA#74-966, also contains ——— Sesame Oil (The *in vivo* bioequivalence waiver request was granted in 1996; the application was approved on April 16, 1998). The ——— Sesame Oil is manufactured by ——— *It passes the same Sesame Oil NF monograph USP specifications* ———



(Pages 123 and 124, Vol. 1.1).

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Apotex Corp. demonstrates that its Fluphenazine Decanoate Injection, 25 mg/mL, falls under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of *in vivo* bioavailability study be granted. The test product, Fluphenazine Decanoate Injection, 25 mg/mL, is deemed bioequivalent to the currently approved Prolixin® Decanoate Injection, 25 mg/mL, manufactured by Apothecon (Squibb).

Hoaithon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 8/25/2000

Concur: Barbara M. Davit Date: 8/31/00
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-918 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/08-23-00/W #75918w.600

Attachments: None

BIOEQUIVALENCY COMMENTS

ANDA: 75-918 APPLICANT: Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection, 25 mg/mL

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,

Barbara M Davit

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

CC: ANDA 75-918
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen

V:\firmsam\apotex\ltrs&rev\75918w.600
Printed in final on / /99

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 8/25/2000
HFD-617/K. Scardina
for HFD-650/ D. Conner 8/31/00

BIOEQUIVALENCY - ACCEPTABLE Submission Date: June 30, 2000

WAIVER (WAI) 01C

Strengths: 25 mg/mL
Outcome: AC

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

AUG 31 2000

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-918 SPONSOR : Apotex Corp.
DRUG AND DOSAGE FORM : Fluphenazine Decanoate Injection
STRENGTH(S) : 25 mg/mL
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A Waiver Request

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HNN DATE : 8/25/00

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 8/25/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 8/31/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-918

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
December 27, 2000

A. 1. **ANDA** 75-918

APPLICANT Apotex Corporation
50 Lakeview Parkway Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAME: Fluphenazine Decanoate Injection USP,

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 25mg/mL solution for intramuscular or subcutaneous injection.

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

5. PHARMACOLOGICAL CATEGORY: Anti-psychotic

B. 1. DATE OF INITIAL SUBMISSION: June 30, 2000
Subject of this review (Received July 3, 2000)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: December 18, 2000

C. REMARKS: The subject drug product is manufactured at Novex Pharma facility located in Richmond Hills, Ontario, Canada. The subject drug product is ———————————— in ———— as a multi-dose solution in 5-mL clear glass vials.

D. CONCLUSIONS: The submission is **not recommended** for approval for lack of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review. The above deficiencies represent a **minor** amendment.

Nrapendra Nath 1/9/01
Nrapendra Nath, Ph.D.

CDR 1/10/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600, V:\microrev\75-918.doc
Initialed by A. High

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
March 2, 2001

A. 1. **ANDA 75-918**

APPLICANT Apotex Corporation
50 Lakeview Parkway Suite 127
Vernon Hills, IL 60061

2. PRODUCT NAME: Fluphenazine Decanoate Injection USP,

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 25mg/mL solution for intramuscular or subcutaneous injection.

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

5. PHARMACOLOGICAL CATEGORY: Anti-psychotic

B. 1. DATE OF INITIAL SUBMISSION: June 30, 2000

2. DATE OF AMENDMENT: February 10, 2001
Subject of this review (Received February 14, 2001)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: March 2, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated January 17, 2001.

D. CONCLUSIONS: The submission is **recommended** for approval for ~~lack of~~ sterility assurance. Specific comments are provided in "E. Review Notes". ash 4/9/01

Nrapendra Nath 3/2/01
Nrapendra Nath, Ph.D.
ash 3/2/01

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600, V:\microrev\75-918a2.doc
Initialed by A. High

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

The following deficiencies were communicated to the firm:

1. Please revise your drug substance release specifications to include USP Identification Test A (IR).

2. Please lower your limits for degradation products other than fluphenazine in your finished product release and stability specifications. The limits should be based on observed values and should not exceed the USP limit of NMT 2.0% for total impurities other than fluphenazine (or NMT 3.0% for total impurities including fluphenazine).

3. Please revise your limit for fluphenazine to NMT 1.0%, rather than NMT 1%, in your finished product release and stability specifications.

The firm will respond via a telephone amendment.

DATE
July 18, 2001

ANDA NUMBER
75-918

TELECON

INITIATED BY:
FDA

PRODUCT NAME
Fluphenazine Decanoate Injection, USP 25 mg/mL

FIRM NAME
Apotex

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Heidi Guzalo

TELEPHONE NUMBER
847-573-9999 x229

FDA Participants
Dave Gill DSG 7/18
John Franolic
Ruby Yu

SIGNATURE
Dave Gill DSG 7/18
John Franolic John Z. Franolic 7/18/01
Ruby Yu 7/19/01

V:\FIRMSAM\APOTEX\TELECONS\75918.TC.071801.doc

CC: T-Con Binder Log
ANDA 75-918

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-918 Applicant APOTEX

Drug Fluphenazine Decanoate Inj Strength 25mg/mL

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

REVIEWER: | DRAFT RECEIPT | FINAL ACTION

1. Project Manager Ruby Yu IV | Date 8/13/01 | Date 8/16/01
Review Support Br | Initials RYu | Initials RYu

Application Summary:

Original Rec'd date 7/3/00 | EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 7/3/00 | Date of EER Status 11-30-2000
Patent Certification (type) II | Date of Office Bio Review 8/31/00
Date Patent/Exclus.expires N/A | Date of Labeling Approv. Sum 6/29/01
Citizens Petition/Legal Case Yes ☐ No ☒ | Date of Sterility Assur. App. 3/2/01
(If YES, attach email from PM to CP coord) | Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ | 30 Day Clock Start ____ End ____
(If YES, check PETS) | Commitment Rcd. from Firm Yes ☐ No
Pediatric Exclusivity Tracking System(PETS) | Modified-release dosage form: Yes ☐ No ☒
Date checked ____ NDA# ____
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 8/16 | Date 8/16
Chemistry Div. I ~~or II~~ | Initials RAC | Initials RAC
Comments:

The CMC section is satisfactory.

3. Frank Holcombe | Date — | Date —
Assoc. Dir. For Chemistry | Initials ____ | Initials ____
Comments: (First generic drug review)

Three (3) ANDAs currently approved. N/A

4. Pat Beers Block | Date ____ | Date ____
Supv. Review Support Branch | Initials ____ | Initials ____
EER Status: Refer to DLPS review below. Ruby Yu 8/17/2001

Bioequivalence sites:

Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status: ____
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status: ____
Reason:

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:

Patent Certification:
Controlled Correspondence/Cit.Pet:
Comments: RLD =

REVIEWER: | DRAFT RECEIPT | FINAL ACTION

5. Nasser Mahmud
Supv. Reg. Support Branch
Date 8/17/01 Initials RW | Date 8/17/01 Initials RW for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant ~~#~~ II
Notify patent holder/NDA holder Yes ☐ No ☐ N/A
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 for each strength: Yes ☐ No ☐
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
RLD = Prolixin Decanoate Injection 25mg/mL Apothecon Inc. NDA 16-727
Comments: there are no unexpired patents or exclusivity on this drug product.

6. Peter Rickman
Acting Director, DLPS
Date 8/17/01 Initials RW | Date 8/17/2001 Initials RW for
Comments: Acceptable EES dated 11/30/00 (Verified 8/17/01). No OAI alerts noted. Bioequivalence waiver granted 2° 21 CFR 320.22(b)(1). Drug product is deemed to be "A" to the RLD. Office-level bio endorsed 8/31/00. Microbiology/sterility assurance found acceptable 3/20/01. FPL found acceptable 6/29/01. CMC acceptable 7/17/01 or 8/14/01. Methods validation is not required - both the API and the drug product are compendial.

7. Robert L. West
Acting Deputy Director, OGD
Date 8/17/01 Initials RW | Date 8/17/01 Initials Robert West

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments:
This application is recommended for approval.

8. Gary Buehler
Acting Director, OGD
Comments:
Date 8/17/01 Initials RW | Date 8/17/2001 Initials Robert West for

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

9. Project Manager Ruby Yu
Review Support Branch
Date 8/17/01 Initials RY | Date 8/17/01 Initials RY

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8:20 AM Time notified of approval by phone (left msg) 8:25 AM Time approval letter faxed

FDA Notification:
8/17 Date e-mail message sent to "OGD approvals" account
8/17 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-918

CORRESPONDENCE

APOTEX CORP.

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

Ack for filing
S. Middleton 8/9/00
505(j)2 yes

June 30, 2000

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Fluphenazine Decanoate Injection, USP
25 mg/mL
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., hereby submits an original abbreviated new drug application (ANDA) for Fluphenazine Decanoate Injection, USP, 25 mg/mL.

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

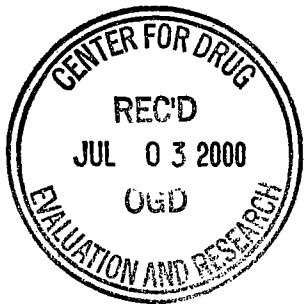
Apotex Corp. hereby certifies that in accordance with 21 CFR 314.94(d)(5), a true field copy of the technical sections of this submission under a burgundy cover is also included.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



ANDA 75-918

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

AUG 14 2000

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.

NAME OF DRUG: Fluphenazine Decanoate Injection USP, 25 mg/mL in 5 mL Multiple Dose Vial

DATE OF APPLICATION: June 30, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 3, 2000

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:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-918
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/NMahmud, Chief, RSB date 8/11/00
HFD-615/Smiddleton, CSO date 8/11/00
Word File
V:\FIRMSAM\APOTEX\LTRS&REV\75918.ACK
F/T mjl/8/9/00
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

DEC 14 2000

ANDA 75-918

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. TEL: 847-573-9999 x223

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 June 30, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluphenazine Decanoate Injection USP, 25 mg/mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 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 MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR 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 you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry and Bioequivalency comments are provided. Labeling and Microbiology comments will be provided when the review is completed.

RYu
12/13/00

DEC 14 2000

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-918 **APPLICANT:** Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection, USP 25 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

5.

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

1. Please be advised that the 27-page Study Protocol SP-AN-750-02.00 appeared in two sections of the ANDA (pp. 626-648, and pp. 730-736). Moreover, Appendix 2 of the Analytical Report AR-750-001-00 is not found after Appendix 1 (it appeared on page 737).

2. Please be advised that the use of in-house analytical methods for testing the drug substance and drug product does not relieve you from meeting the compendial standards. In the event of a dispute, the official USP methods will prevail.

3. The sterility assurance and labeling portion of the ANDA are under review. Deficiencies, if any, will be conveyed to you under separate cover(s).

4. Please submit all available room temperature stability data.

5. Please contact the District Office concerning your vendor qualification protocol for drug substance (p. 170).

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

BIOEQUIVALENCY COMMENTS

ANDA: 75-918 APPLICANT: Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection, 25 mg/mL

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,

Barbara M Davit

for 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

NDA ORIG AMENDMENT
N/As

February 10, 2001

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

MICROBIOLOGY AMENDMENT

RE: ANDA No. 75-918
Fluphenazine Decanoate Injection USP
25 mg/mL

To Whom It May Concern:

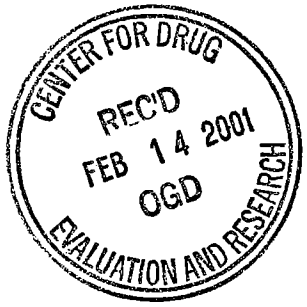
Apotex Corp., is hereby forwarding in duplicate a microbiology amendment in response to the faxed FDA microbiology deficiency letter dated January 17, 2001.

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

February 21, 2001

p/Am

ORIG AMEND...

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

MINOR AMENDMENT

RE: ANDA No. 75-918
Fluphenazine Decanoate Injection USP
25 mg/mL

To Whom It May Concern:

Apotex Corp., is hereby forwarding in duplicate a minor amendment in response to the faxed FDA minor deficiency letter dated December 14, 2000.

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

Sincerely,

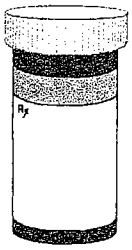
Mark M Lenton (for)

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 23 2001
OGD

2/28/01

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Marcy Macdonald
Apotex Corp.
Fax: 847-573-1001 **Phone**: 847-573-9999

From: Debra M. Catterson
Labeling Reviewer
Fax: 301-443-3847 **Phone**: 301-827-5846

Number of Pages (including cover sheet): 10 **Date**: April 3, 2001

Comments:

Dear Ms. Macdonald,

Attached is the labeling review of your June 30, 2000 submission for ANDA 75-918 for Fluphenazine Decanoate Injection, USP, 25 mg/mL.

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

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

ANDA Number: 75-918

Date of Submission: June 30, 2000 (Original draft labeling)

Applicant's Name: Apotex Corporation

Established Name: Fluphenazine Decanoate Injection USP, 25 mg/mL

Labeling Deficiencies:

1. **CONTAINER** (5 mL Multiple Dose vial):

   Satisfactory in draft.

2. **CARTON** (1 x 5 mL Multiple Dose vial):

   Satisfactory in draft.

3. **INSERT**

   Please refer to pages "62, 63, 64, 65, 68, 72, 73, and 74" of the attached mocked-up copy of your insert labeling for all of the requested labeling revisions.

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.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of firm's mocked-up labeling.

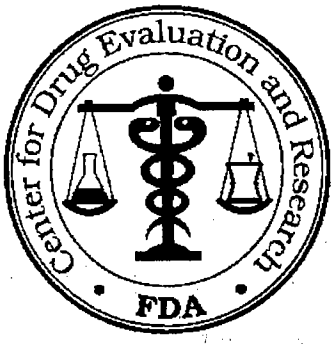
Mocked-up draft labeling was removed from this document.

MINOR AMENDMENT

ANDA 75-918

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)

APR 9 2001



TO: APPLICANT: Apotex Corp.

TEL: 847-573-9999 x223

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 June 30, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluphenazine Decanoate Injection USP, 25 mg/mL.

Reference is also made to your amendment(s) dated: February 21, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (_1_ 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 MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR 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 you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments were sent to you last week.

Rfr 4/9/01

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT APR -9 2001

ANDA: 75-918 **APPLICANT:** Apotex Corp.

DRUG PRODUCT: Fluphenazine Decanoate Injection USP, 25 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

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

1. Please submit all available room temperature stability data.

2. Please contact the District Office concerning your vendor qualification protocol for drug substance (p. 170).

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
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

June 12, 2001

ORIG AMENDMENT
N/AM

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

MINOR AMENDMENT

RE: ANDA No. 75-918
Fluphenazine Decanoate Injection USP
25 mg/mL

To Whom It May Concern:

Apotex Corp., is hereby submitting in duplicate a minor amendment in response to the faxed FDA minor deficiency letter dated April 09, 2001. Additional information not addressed in the deficiency letter is also included.

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

Sincerely,

Marcy Macdonald | H/S

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

9/5/01

APOTEX CORP.

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

June 21, 2001

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

ORIG AMENDMENT
N1AF

LABELING AMENDMENT

RE: ANDA 75-918
Fluphenazine Decanoate Injection, USP
25 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby submitting in duplicate a labeling amendment in response to the FDA deficiency letter dated April 3, 2001.

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

July 31, 2001

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

DRIG AMENDMENT

TELEPHONE AMENDMENT

RE: ANDA No. 75-918
Fluphenazine Decanoate Injection, USP
25 mg/mL

To Whom It May Concern:

Apotex Corp. is hereby submitting in duplicate a telephone amendment in response to the telephone communication with Ruby Yu and her team received on July 18, 2001.

We also certify that as per 21CFR 314.96(2)(b), the enclosed field copy is an exact copy of that provided under the original archive cover.

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

Sincerely,

Marcy Macdonald/ms

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 0 1 2001
OGD