

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074725

**Trade Name : FLUPHENAZINE HCL ORAL SOLUTION
CONCENTRATE 5MG/ML**

**Generic Name: Fluphenazine Hcl Oral Solution Concentrate
5mg/ml**

Sponsor : Pharmaceutical Associates, Inc.

Approval Date: September 16, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074725

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074725

APPROVAL LETTER

SEP 16 1996

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Delaware Street at Perimeter Road
P.O. Box 128
Conestee, SC 29636

Dear Madam:

This is in reference to your abbreviated new drug application dated August 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Fluphenazine Hydrochloride Oral Solution USP (Concentrate), 5 mg/mL.

Reference is also made to your amendment dated August 20, 1996.

We have completed the review of the 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 that your Fluphenazine Hydrochloride Oral Solution USP (Concentrate), 5 mg/mL is bioequivalent and, therefore, therapeutically equivalent to the listed drug (Permitil®, 5 mg/mL, of Schering Corp.).

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

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

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

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

Sincerely yours,

/S/

9/16/96

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

cc: ANDA 74-725
ANDA 74-725/Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-627/NNashed/9
HFD-627/AMueller
HFD-613/LGolson/
HFD-613/AVezza/
HFD-627/WRussell,
F/T by MM Septem
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APPROVAL LETTER

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

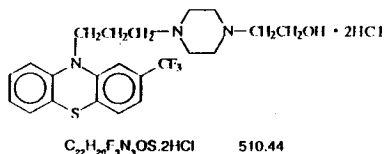
APPLICATION NUMBER 074725

FINAL PRINTED LABELING

Fluphenazine HCL Oral Solution USP (Concentrate)

DESCRIPTION

Fluphenazine hydrochloride is a trifluoromethyl phenothiazine derivative intended for the management of schizophrenia. Each mL of Fluphenazine Hydrochloride Oral Solution (Concentrate), for oral administration, contains fluphenazine hydrochloride, 5 mg; alcohol, 14%. In addition, each mL contains the following inactive ingredients: glycerin, purified water, and sodium benzoate. Fluphenazine hydrochloride has the following structure:



4-[3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol dihydrochloride

CLINICAL PHARMACOLOGY

Fluphenazine hydrochloride 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.

INDICATIONS AND USAGE

Fluphenazine hydrochloride is indicated in the management of manifestations of psychotic disorders.

Fluphenazine hydrochloride 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, in patients receiving large doses of hypnotics, and in comatose or severely depressed states. The presence of blood dyscrasia or liver damage precludes the use of fluphenazine hydrochloride. Fluphenazine hydrochloride 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 the 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.

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

Since there is no adequate experience in children who have received this drug, safety and efficacy in children 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 hydrochloride 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 hydrochloride should be used cautiously in patients exposed to extreme heat or phosphorous insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have been known to occur; and 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 or irreversible dyskinesia should be remembered when patients are on prolonged therapy.

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.

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Abrupt Withdrawal

In general, phenothiazines do not produce psychic dependence; however, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy. Reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

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 hydrochloride.

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. Most often these extrapyramidal symptoms are reversible; however, they may be persistent (see below). 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 fluctuation in blood pressure have been reported with fluphenazine hydrochloride.

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. Levaterenol 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 of 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, have been reported in patients receiving fluphenazine hydrochloride 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.

DOSAGE AND ADMINISTRATION

Depending on the severity and duration of symptoms, total daily dosage for *adult* psychotic patients may range initially from 2.5 to 10 mg and should be divided and given at six- to eight- hour intervals.

The smallest amount that will produce the desired results must be carefully determined for each individual, since optimal dosage levels of this potent drug may vary from patient to patient. In general, the oral dose has been found to be approximately two to three times the parenteral dose of fluphenazine. Treatment is best instituted with a low initial dosage, which may be increased, if necessary, until the desired clinical effects are achieved. Therapeutic effect is often achieved with doses under 20 mg daily. Patients remaining severely disturbed or inadequately controlled may require upward titration of dosage. Daily doses up to 40 mg may be necessary; controlled clinical studies have not been performed to demonstrate safety of prolonged administration of such doses.

When symptoms are controlled, dosage can generally be reduced gradually to daily maintenance doses of 1 to 5 mg, often given as a single daily dose. Continued treatment is needed to achieve maximum therapeutic benefits; further adjustments in dosage may be necessary during the course of therapy to meet the patient's requirements.

For psychotic patients who have been stabilized on a fixed daily dosage of orally administered Fluphenazine Hydrochloride dosage forms, conversion to the long-acting injectable Fluphenazine Decanoate may be indicated [see package insert for Fluphenazine Decanoate Injection for conversion information].

For geriatric patients, the suggested starting dose is 1 to 2.5 mg daily, adjusted according to the response of the patient.

When the Oral Concentrate dosage form is to be used, the desired dose (measured by a calibrated device only) should be added to at least 60 mL (2 fl oz) of a suitable diluent *just prior to administration* to ensure palatability and stability. Suggested diluents include tomato or fruit juice, milk, and uncaffeinated soft drinks. The Oral Concentrate should not be mixed with beverages containing caffeine (coffee, cola), tannins (tea), or pectinates (apple juice) because of the potential incompatibility.

Fluphenazine Hydrochloride Injection USP is useful when psychotic patients are unable or unwilling to take oral therapy.

HOW SUPPLIED

120 mL bottle with a 1 mL safety-cap dropper calibrated at 0.1 mL and in 0.2 mL increments. 5 mg fluphenazine hydrochloride per mL. NDC 0121-0653-04.

Storage

Store at room temperature. Avoid freezing. Protect from light. Keep tightly closed.

CAUTION: Federal law prohibits dispensing without prescription.

Pharmaceutical Associates, Inc. Greenville, SC 29605

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HOW SUPPLIED

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Storage

Store at room temperature. Avoid freezing. Protect from light. Keep tightly closed.

CAUTION: Federal law prohibits dispensing without prescription.

Pharmaceutical Associates, Inc. Greenville, SC 29605

8/96

SEP 1 9 1996

120 mL (4 fl oz) NDC 0121-0653-04

with calibrated dropper

**FLUPHENAZINE HYDROCHLORIDE
ORAL SOLUTION, USP
(CONCENTRATE)**

5 mg/mL

For oral use only

**Caution: Federal law prohibits dispensing
without prescription.**

Pharmaceutical Associates, Inc.
Greenville, SC 29605

**Before Dispensing Replace Cap With Safety
Cap Dropper**

Each mL provides 5 mg fluphenazine hydro-
chloride, alcohol 14%

**MEASURE DOSE WITH CALIBRATED
DEVICE ONLY**

DILUTE DOSE BEFORE ADMINISTRATION

Usual Dosage: See package insert for dosage
information.

Protect from light

Keep tightly closed

Store at room temperature; avoid freezing

Pharmaceutical Associates, Inc.
Greenville, SC 29605

EXP
Lot

SEP 16 1996

120 mL (4 fl oz) NDC 0121-0653-04
with calibrated dropper

**FLUPHENAZINE HYDROCHLORIDE
ORAL SOLUTION, USP
(CONCENTRATE)
5 mg/mL**

120 mL (4 fl oz) NDC 0121-0653-04
with calibrated dropper

**FLUPHENAZINE HYDROCHLORIDE
ORAL SOLUTION, USP
(CONCENTRATE)
5 mg/mL**

For oral use only

**Before Dispensing Replace Cap
With Safety Cap Dropper**

**Caution: Federal law prohibits
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**Pharmaceutical Associates, Inc.
Greenville, SC 29605**

SEP 16 1996

**FLUPHENAZINE HYDROCHLORIDE
ORAL SOLUTION, USP
(CONCENTRATE)**

Each mL provides 5 mg fluphenazine
hydrochloride; alcohol 14%

**MEASURE DOSE WITH
CALIBRATED DEVICE ONLY**

**DILUTE DOSE BEFORE
ADMINISTRATION**

Usual Dosage: See package insert
for dosage information.

Protect from light

Keep tightly closed

**Store at room temperature; avoid
freezing**

Pharmaceutical Associates, Inc.
Greenville, SC 29605

EXP
Lot

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074725

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-725

3. NAME AND ADDRESS OF APPLICANT

Pharmaceutical Associates, Inc.
P.O. Box 128
Conestee, SC 29636

4. LEGAL BASIS FOR SUBMISSION

The firm claims that to the best of their knowledge they certify that with respect to each patent which claims the listed drug Permitil Oral Concentrate, such patent has expired.

The exclusivity is not applicable for the listed drug Permitil.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluphenazine Hydrochloride

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

N/A

9. AMENDMENTS AND OTHER DATES:

5/24/95

8/20/96

10. PHARMACOLOGICAL CATEGORY

For the management of schizophrenia

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

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13. DOSAGE FORM

Oral Solution

14. POTENCY

5 mg/mL

15. CHEMICAL NAME AND STRUCTURE

4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol]dihydrochloride.

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 9/5/96

Supervisor: A.Mueller for Paul Schwartz, Ph.D./9-6-96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074725

BIOEQUIVALENCE REVIEW(S)

ANDA 74-725

Pharmaceutical Associates, Inc.
Attention: Jane Hicks
P.O. BOX 128
Conestee SC 29636
|||||

APR 11 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Fluphenazine Hydrochloride Oral Solution USP (Concentrate), 5 mg/mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 4 1996 DW

Fluphenazine HCl
Oral Solution,
5 mg/mL
ANDA # 74-725
Reviewer: L. Chuang

Pharmaceutical Associates, Inc.
Conestee, South Carolina
Submission Date:
August 9, 1995

Review of a Waiver Request

This is an amendment to the pending ANDA #74-725. The original submission of this ANDA (received 08/10/95), was **refused to file** by the Agency because the firm failed to properly identify the reference listed drug in the application.

The reference listed drug identified in Supplement 7 of the *Approved Drug Products with Therapeutic Equivalence Evaluation, 15th Edition*, is **Permitil 5 mg/mL manufactured by Schering** while the firm reported the reference listed drug as **Prolixin^R Oral Concentrate, 5 mg/mL, manufactured by Apothecon.**

For the administration of fluphenazine HCl 5 mg/mL oral solution, the desired dose (measured by a calibrated device only) should be added to at least 60 mL of diluent just prior to administration. The initial daily doses are 2.5-10 mg divided into 3-4 times daily. Daily dose up to 40 mg daily may be necessary.

The comparative formulations of the test drug product and Permitil are presented below:

Ingredients	Fluphenazine HCl Oral Solution (Pharmaceutical Asso.)	Permitil Concentrate (Schering)
	Per mL	Potency
Fluphenazine HCl	5 mg	5 mg/mL
Alcohol	(b)4 - Confidential Business	
Sodium Benzoate		
Glycerin		
Sodium Hydroxide		
propylparaben		
Sodium Phosphate, Monobasic		
methylparaben		

Purified Water	q.s. to 1 mL	q.s. to 1 mL
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The firm requests the Agency to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of the test drug product because it meets the provisions of 21 CFR 320.22(b) (3).

Comments:

1. Fluphenazine HCl is freely soluble in water, hence the test formulation is an oral solution.
2. Both test and reference drug products contain 5 mg/mL of fluphenazine HCl.
3. The absence of sodium hydroxide to adjust pH, methylparaben and propylparaben as preservatives, and sodium phosphate monobasic (0.7%) in the test formulation should not significantly affect the absorption of fluphenazine.
4. The presence of sodium benzoate (2 mg/mL) as preservative, high concentration of alcohol (14% in the test and 1% in the reference), and 35% glycerin in the test formulation are probably acceptable since the test formulation will undergo at least 22.5-fold dilution (calculated at maximum daily dose of 40 mg divided into 3 doses) during oral administration. The final concentrations of the 3 ingredients mentioned above would be 0.01%, 0.6% and 1.5%, respectively, which are all within ranges published in the Inactive Ingredient Guide (10/93).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. demonstrates that its fluphenazine oral solution, 5 mg/mL, falls under 21 CFR 320.22(b) (3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Permitil[®], marketed by Schering.

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Business

3/27/96

Division of Bioequivalence
Review Branch I