CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040187

Trade Name : THIORIDAZINE HYDROCHLORIDE ORAL SOLUTION USP 30MG/ML (CONCENTRATE)

Generic Name: Thioridazine Hydrochloride Oral Solution USP 30mg/ml (concentrate)

Sponsor : Pharmaceutical Associates, Inc.

Approval Date: August 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040187

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040187

APPROVAL LETTER

"ON

ANDA 40-187

AUG 28 1997

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

Dear Madam:

This is in reference to your abbreviated new drug application dated May 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Thioridazine Hydrochloride Oral Solution USP, 30 mg/mL (Concentrate).

Reference is also made to your amendments dated June 6, 1996; April 21, July 10, July 30, 1997, and August 18, 1997.

We have completed the review of this 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 Thioridazine Hydrochloride Oral Solution USP, 30 mg/mL (Concentrate) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (Mellaril® Oral Solution, 30 mg/mL (Concentrate) of Novartis Pharmaceutical Corporation).

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. 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-240). Please do not use Form FDA-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-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040187

FINAL PRINTED LABELING

NDC 0121-0661-04

Thioridazine Hydrochloride Oral Solution USP (Concentrate)

30 mg/mL

Each mL contains:
Thioridazine HCl, USP..... 30 mg
Alcohol..... 3% by volume

CAUTION: Federal law prohibits dispensing without prescription.

Store and Dispense: Below 86°F(30°C); in a tight, light resistant containers defined in the USP.

4fl oz (118mL)

pai Pharmaceutical Associates, Inc.
Greenville,SC 29605

Usual Dosage: See package insert for dosage information.

It is Recommended that theConcentrate be used only for severe neuropsychiatric conditions.

Lot No:

Exp Date:

Immediately before administration, dilute the dose of Concentrate with distilled-water, acidified tap water, or suitable juices.

Suggested Dilution; 25 mg dose in 2 teaspoonfuls of diluent-liquid. For higher doses increase the volume of diluent.

4 fl oz (118 mL)

Thioridazine Hydrochloride Oral Solution USP (Concentrate)

30 mg/mL

3 1997

NDC 0121-0661-04
NSN 6505-00-059-3497

Thioridazine Hydrochloride Oral Solution, USP (Concentrate)

30 mg/mL

Each mL contains:
Thioridazine HCl, USP..... 30 mg
Alcohol..... 3% by volume

Usual Dosage:
See package insert for details.

DILUTE BEFORE USE.

It is Recommended that the Concentrate be used only for severe neuropsychiatric conditions.

CAUTION: Federal law prohibits dispensing without prescription.

Store and Dispense: Below 86°F (30°C); in a tight, light resistant container as defined in the USP.

4 fl oz (118 mL)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

TURN OTHER END UP TO OPEN

KEEP THIS END UP

30 mg/mL

Thioridazine
Hydrochloride
Oral Solution USP
(Concentrate)

4 fl oz (118 mL)

Thioridazine Hydrochloride Oral Solution USP (Concentrate)

30 mg/mL

NDC 0121-0661-04
NSN 6505-00-059-3497

Thioridazine Hydrochloride Oral Solution, USP (Concentrate)

30 mg/mL

Each mL contains:
Thioridazine HCl, USP..... 30 mg
Alcohol..... 3% by volume

Usual Dosage:
See package insert for details.

DILUTE BEFORE USE.

It is Recommended that the Concentrate be used only for severe neuropsychiatric conditions.

CAUTION: Federal law prohibits dispensing without prescription.

Store and Dispense: Below 86°F (30°C); in a tight, light resistant container as defined in the USP.

4 fl oz (118 mL)

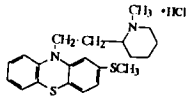
pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

Thioridazine Hydrochloride Oral Solution, USP

(Concentrate) 30 mg/mL

DESCRIPTION

Thioridazine hydrochloride is 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine monochloride. The presence of a thiomethyl radical ($S\text{-}CH_3$) in position 2, conventionally occupied by a halogen, is unique and could account for the greater toleration obtained with recommended doses of thioridazine as well as a greater specificity of psychotherapeutic action.



$C_{21}H_{26}N_2S_2 \cdot HCl$ M.W. = 407.05

30 mg Concentrate

Each mL, for oral administration, contains: 30 mg Thioridazine hydrochloride, USP and 3% alcohol. Inactive ingredients: flavor, methylparaben, propylparaben, purified water, and sorbitol solution. May contain sodium hydroxide or hydrochloric acid to adjust pH.

CLINICAL PHARMACOLOGY

Thioridazine is effective in reducing excitement, hypermotility, abnormal initiative, affective tension, and agitation through its inhibitory effect on psychomotor functions. Successful modification of such symptoms is the prerequisite for, and often the beginning of, the process of recovery in patients exhibiting mental and emotional disturbances. Thioridazine's basic pharmacological activity is similar to that of other phenothiazines, but certain specific qualities have come to light which support the observation that the clinical spectrum of this drug shows significant differences from those of the other agents of this class. Minimal antiemetic activity and minimal extrapyramidal stimulation, notably pseudoparkinsonism, are distinctive features of this drug.

INDICATIONS AND USAGE

For the management of manifestations of psychotic disorders.

For the short-term treatment of moderate to marked depression with variable degrees of anxiety in adult patients and for the treatment of multiple symptoms such as agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients.

For the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance.

CONTRAINDICATIONS

In common with other phenothiazines, thioridazine is contraindicated in severe central nervous system depression or comatose states from any cause. It should also be noted that hypertensive or hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration.

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 Information for Patients and ADVERSE REACTIONS.)

It has been suggested in regard to phenothiazines in general, that people who have demonstrated a hypersensitivity reaction (e.g. blood dyscrasias, jaundice) to one may be more prone to demonstrate a reaction to others. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g. anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorous insecticides. Physicians should carefully consider benefit versus risk when treating less severe disorders.

Reproductive studies in animals and clinical experience to date have failed to show a teratogenic effect with thioridazine hydrochloride. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, thioridazine hydrochloride should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

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.

PRECAUTIONS

Leukopenia and/or agranulocytosis and convulsive seizures have been reported but are infrequent. Thioridazine hydrochloride has been shown to be helpful in the treatment of behavioral disorders in epileptic patients, but anticonvulsant medication should also be maintained. Pigmentary retinopathy, which has been observed primarily in patients taking larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication may be reduced by remaining within the recommended limits of dosage.

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension in view of the fact that phenothiazines may induce a reversed epinephrine effect on occasion. Should a vasoconstrictor be required, the most suitable are norephinephrine and phenylephrine.

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.

Concurrent administration of propranolol (100 to 800 mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50% to 400%) and its metabolites (approximately 80% to 300%).

It is recommended that a daily dose in excess of 300 mg be reserved for use only in severe neuropsychiatric conditions.

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

In the recommended dosage ranges with thioridazine hydrochloride most side effects are mild and transient.

Central Nervous System: Drowsiness may be encountered on occasion, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare.

Autonomic Nervous System: Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor have been seen.

Endocrine System: Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema have been described.

Skin: Dermatitis and skin eruptions of the urticarial type have been observed infrequently. Photosensitivity is extremely rare.

Cardiovascular System: ECG changes have been reported. (See Phenothiazine Derivatives; Cardiovascular Effects)

Other: Rare cases described as parotid swelling have been reported following administration of thioridazine hydrochloride.

Phenothiazine Derivatives

It should be noted that efficacy, indications, and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines. The most common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leukopenia in the geriatric population. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including thioridazine hydrochloride. To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the WARNINGS section and below.

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. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, 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, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states. More recently a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

DOSAGE AND ADMINISTRATION

Dosage must be individualized according to the degree of mental and emotional disturbance. In all cases, the smallest effective dosage should be determined for each patient.

Adults

Psychotic Manifestations: The usual starting dose is 50 to 100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose. The total daily dosage ranges from 200 to 800 mg, divided into two to four doses.

For the short-term treatment of moderate to marked depression with variable degrees of anxiety in adult patients and for the treatment of multiple symptoms such as agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients.

The usual starting dose is 25 mg three times a day. Dosage ranges from 10 mg two to four times a day in milder cases to 50 mg three or four times a day for more severely disturbed patients. The total daily dosage range is from 20 mg to a maximum of 200 mg.

Children

Thioridazine hydrochloride is not intended for children under 2 years of age. For children ages 2 to 12 the dosage of thioridazine hydrochloride ranges from 0.5 mg to a maximum of 3 mg/kg/day. For children with moderate disorders, 10 mg two or three times a day is the usual starting dose. For hospitalized, severely disturbed, or psychotic children, 25 mg two or three times daily is the usual starting dose. Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum has been reached.

HOW SUPPLIED

Thioridazine Hydrochloride Oral Solution, USP Concentrate

30 mg/mL

A clear straw-yellow liquid with a cherry-like odor. Each mL contains 30 mg thioridazine hydrochloride, USP, alcohol, 3% by volume. Immediate Container: bottles of 4 fl. oz.(118 mL) as follows: 4 fl. oz. bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg, and 50 mg of thioridazine HCl, USP, NDC 0121-0661-04.

Store and Dispense

Below 86°F (30°C); in a tight, light resistant container as defined in the USP.

The concentrate may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be so diluted just prior to administration - preparation and storage of bulk dilutions is not recommended.

Caution: Federal Law Prohibits Dispensing Without Prescription

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

6/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040187

CHEMISTRY REVIEW(S)

DN

1. CHEMISTRY REVIEW NO.3

2. ANDA # 40-187

3. NAME AND ADDRESS OF APPLICANT

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

4. LEGAL BASIS FOR SUBMISSION

The firm has indicated that in their opinion and to the best of their knowledge with respect to each patent which claims the listed drug has expired and no exclusivity has not been granted for the listed drug Mellaril.

5. SUPPLEMENT(s)

Original 5/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Thioridazine Hydrochloride

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 6/6/96
Amendment 4/21/97
Amendment 7/10/97
Amendment 7/30/97
Amendment 8/18/97

10. PHARMACOLOGICAL CATEGORY

Antipsychotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM

Solution

14. POTENCY

30 mg/mL

15. CHEMICAL NAME AND STRUCTURE

2-methylmercapto-10-[2-(N-methyl-2-piperdyl)ethyl] phenothiazine

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 8/19/97

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 40-187
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed, Ph.D./8-5-97
HFD-627/P.Schwartz, Ph.D/8-5-97
X:\NEW\FIRMSNZ\PHARMACE\LTRS&REV\40-187.4
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040187

BIOEQUIVALENCE REVIEW(S)

ANDA 40-187

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. BOX 128
Conestee SC 29636

SEP 26 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 Thioridazine Hydrochloride Oral Solution USP, 30 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

SEP 13 1996

Thioridazine HCl Oral Solution
USP Concentrate 30 mg/mL
ANDA #40-187
Reviewer: Moheb H. Makary
WP 40187W.596

Pharmaceutical Associates
Conestee, South Carolina
Submission Date:
May 15, 1996

Review of a Request for Waiver of in vivo Bioequivalence Requirements

Objective:

The firm has requested a waiver of the requirement for submission of in vivo bioequivalence evidence as provided under CFR 320.22 (b)(3). The test product is an oral solution (concentrate) containing the same active ingredient (Thioridazine HCl) in the same concentration (30 mg/mL) as the reference approved product, Mellaril^{R} (Thioridazine HCl Oral Solution USP), 30 mg/mL (Sandoz). The test formulation does not contain any inactive ingredients known to significantly affect absorption of the active ingredient (Table I).

Thioridazine HCl Oral Solution is indicated for the management of manifestations of psychotic disorders.

Thioridazine HCl Oral Solution, 30 mg/mL is coded AA in the Orange Book.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc., demonstrates that its Thioridazine HCl Oral Solution, USP Concentrate 30 mg/mL, falls under 21 CFR 320.22 (b)(3).of the Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study requirements for Pharmaceutical's Thioridazine HCl Oral Solution, USP Concentrate 30 mg/mL, is granted. From the bioequivalence point of view the Division of Bioequivalence deems the test Oral Concentrate product to be bioequivalent to Mellaril^{R} (Thioridazine HCl Oral Solution USP), 30 mg/mL manufactured by Sandoz.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III