

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040126

Trade Name : THIORIDAZINE HCL ORAL SOLN CONC

**Generic Name: Thioridazine Hcl Oral Solution Concentrate
100mg/ml**

Sponsor : Hi-Tech Pharmacal Co., Inc.

Approval Date: August 16, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040126

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| Final Printed Labeling | X | | | |
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040126

APPROVAL LETTER

ANDA 40-126

AUG 16 1996

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

Reference is made to your abbreviated new drug application dated December 9, 1994, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Thioridazine Hydrochloride Oral Solution USP (Concentrate), 100 mg/mL.

Reference is also made to your amendment dated August 2, 1996.

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 that your Thioridazine Hydrochloride Oral Solution USP, 100 mg/mL is bioequivalent and, therefore therapeutically equivalent, to the listed drug (Mellaril^R Oral Solution, 100 mg/mL, of Sandoz Pharmaceuticals Corporation, Division of Sandoz Inc.).

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,

/S/

8/16/96

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

CC: ANDA 40-126
ANANDA 40-126/Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/PSavino
HFD-610/J.Phillips

Endorsements:

/S/

APPROVAL LETTER

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040126

FINAL PRINTED LABELING

MINI GRAPHICS
SPECIALIZING IN PHARMACEUTICAL
PACKAGE INSERTS AND ROLL LABELS

Tel: (516) 223-6464
Fax: (516) 223-6486

45 St. John's Place
Freeport, New York 11520

CUSTOMER: HI-TECH
 PLATE #: 3137-1
 JOB #: 3137
 P.O. #: 13430-A
 MISC. CODE #: 038
 ATTN: JOANNE CURRI

PROOF #: 4
 LABEL SIZE: 2.25" X 5.25"
 PROOF SIZE (%): 100
 DATE OUT: 08/24/95

UPC CODE SPECS.
 100 %
 -.002 B.W.A.

COLORS
 PMS BLACK
 PANTONE GREEN
 PMS 295 BLUE
 Unvarnished Area

H-T
 NDC 50383-038-04
Thioridazine HCl
Oral Solution, USP
CONCENTRATE
100 mg/mL
 CAUTION: Federal law prohibits
 dispensing without prescription.
4 fl oz (118 mL)
HI-TECH PHARMACAL CO., INC.
 Amityville, NY 11701

Thioridazine HCl
 Oral Solution, USP
 CONCENTRATE

Each mL contains:
 Thioridazine HCl 100 mg
 Alcohol 4.2%
 USUAL DOSAGE: See package insert for dosage
 information.
 It is recommended that the Concentrate be used
 only for severe neuropsychiatric conditions.
 Immediately before administration, dilute the
 dose of Concentrate with distilled water, acidified
 tap water or suitable juices.
 Suggested Dilution: 25 mg dose in 2 teaspoons of
 diluent-liquid. For higher doses increase the
 volume of diluent.
 Dispense in a light, light-resistant container as
 defined in the USP.
 Store at controlled room temperature 15°-30°C
 (59°-86°F).

7 40017-038-04 6

O.K. TO PRINT
 SUBMIT ADDITIONAL PROOFS

Production delivery 2 - 3 weeks from receipt of O.K. TO PRINT.

AUTHORIZED BY: _____

DATE: _____

Man...

LOT NO. & EXP. DATE



NDC: 50383-038-04

**Thioridazine
HCl Oral
Solution, USP
CONCENTRATE
100 mg/mL**

Each mL contains:
Thioridazine HCl, USP 100 mg
Alcohol 4.2%

Usual Dosage: See package insert for details.
It is recommended that the Concentrate be used only for severe neuropsychiatric conditions.
CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

4 fl. oz (118 mL)



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HCl Oral
Solution, USP
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HI-TECH PHARMACAL CO. INC.
Amityville, NY 11701

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APPROVED AUG 15 1994

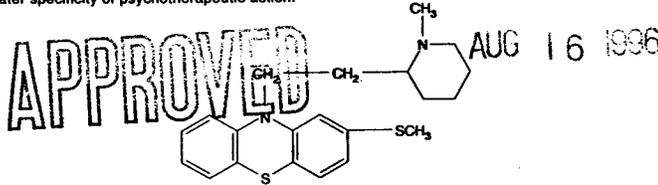
THIORIDAZINE HYDROCHLORIDE ORAL SOLUTION, USP CONCENTRATE

30 mg/mL and 100 mg/mL

DESCRIPTION

Thioridazine is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl)ethyl] phenothiazine.

The presence of a thiomethyl radical (S-CH₃) 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.



C₂₁H₂₆N₂S₂ · HCl

407.05

Each mL, for oral administration, contains 30 mg thioridazine hydrochloride and alcohol 3%, or 100 mg thioridazine hydrochloride and alcohol 4.2%. Inactive ingredients include: flavor, methylparaben, propylparaben, purified water, and sorbitol solution. May contain sodium hydroxide or hydrochloric acid to adjust the pH. In addition, the 100 mg/mL also contains the inactive ingredients glycerin and sucrose.

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 phosphorus 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. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, thioridazine 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 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

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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 norepinephrine 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 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.

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.

Hepatotoxicity: 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. 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 is not intended for children under 2 years of age. For children aged 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 is a clear, viscous cherry flavored liquid available in 4 fl oz (NDC 50383-039-04) amber PET containers with a child-resistant cap supplied with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of thioridazine hydrochloride, USP.

Thioridazine Hydrochloride Oral Solution, USP (Concentrate) 100 mg/mL is a clear, viscous strawberry flavored liquid available in 4 fl oz (NDC 50383-038-04) amber PET containers with a child-resistant cap supplied with an accompanying dropper graduated to deliver 100 mg, 150 mg and 200 mg of thioridazine hydrochloride, USP.

Store at controlled room temperature 15°-30°C (59°-86°).

Dispense 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.

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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 is not intended for children under 2 years of age. For children aged 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 is a clear, viscous cherry flavored liquid available in 4 fl oz (NDC 50383-039-04) amber PET containers with a child-resistant cap supplied with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of thioridazine hydrochloride, USP.

Thioridazine Hydrochloride Oral Solution, USP (Concentrate) 100 mg/mL is a clear, viscous strawberry flavored liquid available in 4 fl oz (NDC 50383-038-04) amber PET containers with a child-resistant cap supplied with an accompanying dropper graduated to deliver 100 mg, 150 mg and 200 mg of thioridazine hydrochloride, USP.

Store at controlled room temperature 15°-30°C (59°-86°).

Dispense 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.

HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

Rev. 4/96
MG #11191

4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040126

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 40-126

DRUG PRODUCT: Thioridazine Hydrochloride Oral Solution USP, 100 mg/mL

FIRM: Hi-Tech Pharmacal Co., Inc.

DOSAGE FORM: Oral Solution **STRENGTH:** 100mg/mL

CGMP: EER is currently unacceptable for all facilities, 1-22-96.

BIO: Satisfactory as per review of K. Dhariwal, 5-13-96. Hi-Tech's request for a bio-waiver under 21 CFR 320.22(b)(2) is satisfactory.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

The drug substance and drug product are compendial monographs in the US Pharmacopeia. No validation studies are required.

STABILITY:

The containers in the stability study are identical to those in the container section.

LABELING:

Container, carton and insert labeling have been approved (L. Golson, 5-3-96).

STERILIZATION VALIDATION (IF APPLICABLE):

Non sterile drug product. No validation review required.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

The size of the bio/exhibit batch was (b)4 - Lot 301-038, pages 382-482 of the original application. The intended sizes of production batches are (b)4 - (b)4 - (b)4 - Confidential and (b)4 - See pages 351-378 of the original application for copies of the blank production records. Packaging records have been included for the four ounce containers of drug product. (b)4 - of the exhibit batch was packaged with losses of approximately (h)4 see page 397).

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batch is the bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batches are **(b)4 - Confidential**
The manufacturing process is the same as the exhibit batch.

CHEMIST: A.J. Mueller, Ph.D.

DATE: 5-16-96

SUPERVISOR: P. Schwartz, Ph.D.

DATE: 5-20-96

X:\NEW\FIRMSAM\HITECH\LTRS&REV\40126N00.AP3
May 16, 1996

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 3 (final approval)
2. ANDA # 40-126
3. NAME AND ADDRESS OF APPLICANT
Hi-Tech Pharmcal Co., Inc
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701
4. LEGAL BASIS OF SUBMISSION:
No Patent or any marketing exclusivity rights are in effect.
5. SUPPLEMENT (s)
N/A
6. PROPRIETARY NAME

Thioridazine Hydrochloride Oral Solution, USP Concentrate 100 mg/mL
7. NONPROPRIETARY NAME

Thioridazine Hydrochloride Oral Solution USP, 100 mg/mL
8. SUPPLEMENT (s) PROVIDE (s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Applicant:
12/09/94 Original Submission
08/30/95 Amendment
04/08/96 Amendment (Bio issues)
04-18-96 Amendment (CMC issues)

FDA:
01/18/95 Acknowledgement
05/26/95 NA Letter
07/31/95 NA Letter (Bio)
03/25/96 NA Letter (CMC)
10. PHARMACOLOGICAL CATEGORY
Antipsychotic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF (s)

Listed Drugs: Mellaril® Solution
 Holder: Sandoz Pharmaceuticals
 NDA Number: 11-808
 For DMF's details please refer to item #37 of this review.

13. DOSAGE FORM
 Liquid (Oral)

14. STRENGTH
 100 mg/mL

15. CHEMICAL NAME AND STRUCTURE
 10H-Phenothiazine, 10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylthio)-, monohydrochloride.
 Mol formula C₂₁H₂₆N₂S₂.HCl, Mol. Wt 407.03
 For structure see USP 23, p-1541.

16. COMMENTS
 None.

17. CONCLUSIONS AND RECOMMENDATIONS
 The application is approvable pending acceptable EER. **EER is currently unacceptable for all facilities, 1-22-96.**

18. RECORDS AND REPORTS
 N/A

| | |
|---|--|
| 19. <u>REVIEWER:</u> A.J. Mueller, Ph.D. | <u>DATE COMPLETED:</u> May 15, 1996 |
| Endorsed by P. Schwartz, Ph.D. | May 20, 1996 |

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040126

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 40-126 SPONSOR: Hi-Tech Pharmacal Co., Inc.
DRUG: Thioridazine Hydrochloride
DOSAGE FORM: Oral Solution (Concentrate)
STRENGTHS/(s): 100 mg/mL, 4 fl oz bottle
TYPE OF STUDY: Single/Multiple Waiver
STUDY SITE:

NOT A FIRST GENERIC

STUDY SUMMARY: The waiver of *in vivo* bioequivalence study is granted under 21 CFR 320.22 (b)(3). ~~However, the Division of Chemistry should review and consider the acceptance of the~~
(b)4 - Confidential Business ~~before final approval of the~~
product. *See review dated 5/8/96, page 2, paragraph 4, under Comments*

MDJ
5/22/96

16
5/22/96

DISSOLUTION: Not applicable

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: **/S/** DATE 5/21/96

BRANCH CHIEF: Shrinivas Nerurkar, Ph.D., BRANCH: II

INITIAL: **/S/** 5/21/1996

DIRECTOR
DIVISION **/S/** E: Keith Chan, Ph.D

INITIAL: **/S/** DATE 5/22/96

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: N/A DATE _____

ANDA 40-126

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityvile NY 11701
|||||

MAY 13 1996

Dear Sir:

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 (Concentrate), 100 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,

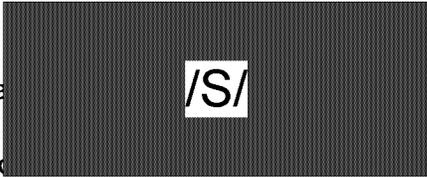
A rectangular area with a dark, textured background, containing a white box with the initials "/S/".

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

cc: ANDA 40-126, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
Letter Out, Bio Acceptable

Endorsements:

K. Dhariwa
R. Patnaik
M. Anderson



/S/

DRAFTED: STM 05/09/96 X:\WPFILE\BIO\FINAL\N40126.APP

MAY 6 1996 9 N

Thioridazine Hydrochloride
Oral Solution (Concentrate)
100 mg/mL, 4 fl oz. bottle
ANDA # 40-126
Reviewer: Kuldeep R. Dhariwal
File name: 40126W.496

Hi-Tech Pharmacal Co., Inc.
369 Bayview Avenue
Amityville, N.Y. 11701
Submission Date:
April 8, 1996

Response to Review of Waiver Request

The firm submitted a request for waiver of *in vivo* bioavailability/bioequivalence study for Thioridazine Hydrochloride Oral Solution (Concentrate), 100 mg/mL on December 9, 1994. The firm had also submitted similar request for another strength of Thioridazine Hydrochloride Oral Solution, 30 mg/mL under separate submission (File names 40126W.D94 and 40125W.D94). Both waiver requests were denied. The deficiency comments were communicated to the firm. The firm has now submitted the response as amendments.

Response:

Comment 1. Glycerin and Sucrose are listed in the composition of reference listed drug, see Physician's Desk Reference, 1995, Mellaril Oral Solution (Concentrate) 100 mg/mL (Sandoz). These ingredients are also included in the list of components on page 83 of the ANDA, and other places in the submission. However, both of these ingredients are not listed in the side-by-side qualitative comparison of formulations on page 81. Please clarify.

Response: Glycerin and sucrose were inadvertently omitted from the side-by-side qualitative comparison of formulations on page 81. The firm has provided revised formulation comparisons including glycerin and sucrose.

Comment 2. The composition of (b)4 - Confidential Business was not submitted, and is required for review.

a. As provided under 21 CFR 320.22(b)(3)(iii), as a condition of approving a waiver the test product shall not contain any inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

b. As provided under 21 CFR 314.94(a)(9)(ii), an applicant shall identify and characterize the inactive ingredients in their proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.

Please compare and contrast the formulations of the test product and reference listed drug, if differences in formulation exist, evidence should be provided that demonstrates that such differences will not significantly affect absorption of the active drug ingredient or active moiety, or affect the safety of the proposed drug product.

Response: The firm has submitted the composition of [REDACTED] (b)4 - Confidential including the FEMA numbers and CFR references. The firm states that this flavor will not affect the absorption of the active drug ingredient or affect the safety of the proposed drug product.

Comments:

1. NOT TO BE RELEASED UNDER FOI: [REDACTED] (b)3 - Other Statutes [REDACTED] is not listed in IIG 1995. In the Division of Chemistry, this ANDA was reviewed by Vilayat A. Sayeed. This chemistry reviewer had also asked for the same information (composition of [REDACTED] (b)4 - [REDACTED] in his deficiency comments. Dr. Sayeed will not be reviewing the response submitted by the firm as he has been promoted to Team Leader. The new chemistry reviewer for this ANDA has not yet been designated. This reviewer discussed the composition of [REDACTED] (b)4 - [REDACTED] with Paul Schwartz. All the ingredients of [REDACTED] are FEMA (Flavor Extracts Manufacturers Association) listed and have CFR references. Therefore, in his opinion this flavor is considered safe. General discussion with other chemistry reviewers about other ANDA's suggest that if the ingredients are FEMA listed and have CFR references, they are considered safe. Based on this judgement, this reviewer considers that [REDACTED] (b)4 - [REDACTED] used by the firm is OK. However, the final decision on accepting this ingredient in the formulation should be carefully considered by the Division of Chemistry.

2. Firm's response to chemistry deficiencies have not yet been reviewed by the Division of Chemistry.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Hi-Tech Pharmacal Co. demonstrates that thioridazine hydrochloride oral solution (concentrate), 100 mg/mL falls under 21 CFR 320.22 (b)(3) of the bioavailability/bioequivalence regulations. The waiver of the *in vivo* bioequivalence study

requirements for the 100 mg/mL oral solution, concentrate (test product) is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Mellaril® oral solution (concentrate), 100 mg/mL manufactured by Sandoz Pharmaceuticals Corporation.

2. The Division of ~~Chemistry~~ should ~~review~~ and consider the acceptance of the ~~(b)4 - Confidential~~ before final approval of the product.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/

Date 5/6/96

Concur:

/S/

Date _____

Director, Division of Bioequivalence

cc: ANDA #40-126 (original), HFD-600 (Hare), HFD-630, HFD-655 (Nerurkar, Dhariwal), Drug File, Division File

Draft: 042596; Final 050396

JUL 31 1995

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

Reference is made to the request for a waiver of *in vivo* bioequivalence, submitted on December 9, 1994, for Thioridazine Hydrochloride Oral Solution USP (Concentrate), 100 mg/mL.

The Office of Generic Drugs has reviewed the waiver request and has found it to be incomplete for the following reasons:

1. Glycerin and Sucrose are listed in the composition of reference listed drug, see Physicians' Desk Reference, 1995, Mellaril Oral Solution (Concentrate) 100 mg/mL (Sandoz). These ingredients are also included in the list of components on page 83 of the ANDA, and other places in the submission. However, both of these ingredients are not listed in the side-by-side qualitative 'comparison of formulations' on page 81. Please clarify.
2. The composition of **(b)4 - Confidential Business** was not submitted, and is required for review.
 - a. As provided under 21 CFR 320.22(b)(3)(iii), as a condition of approving a waiver the test product shall not contain any inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.
 - b. As provided under 21 CFR 314.94(a)(9)(ii), an applicant shall identify and characterize the inactive ingredients in their proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.

Please compare and contrast the formulations of the test product and reference listed drug, if differences in formulation exist, evidence should be provided that demonstrates that such differences will not significantly affect absorption of the active drug ingredient or active moiety, or affect the safety of the proposed drug product.

As described under 21 CFR 314.96 an action which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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

JUL 25 1995

Thioridazine Hydrochloride
Oral Solution (Concentrate)
100 mg/mL, 4 fl oz bottle
ANDA # 40-126
Reviewer: Kuldeep R. Dhariwal
File Name: 40126W.D94

Hi-Tech Pharmacal Co., Inc.
369 Bayview Avenue
Amityville, N.Y. 11701

Submission Date:
December 9, 1994

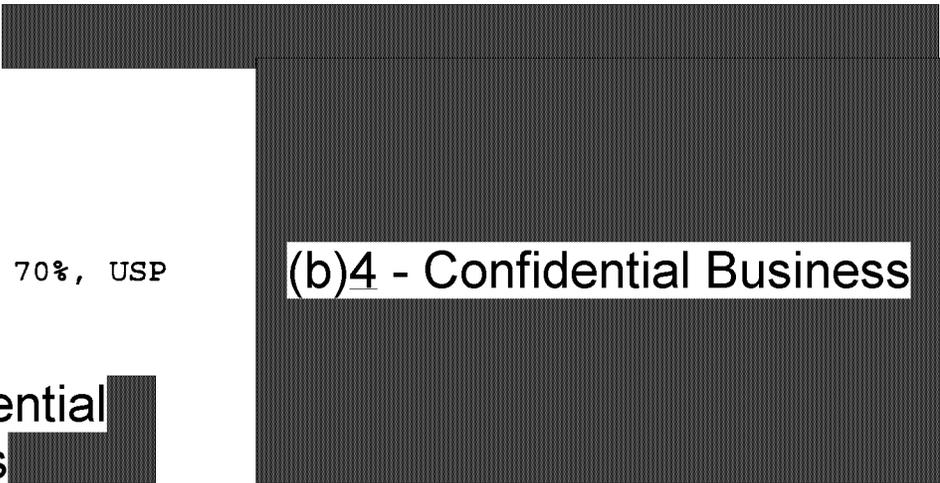
REVIEW OF A WAIVER REQUEST

INTRODUCTION:

The firm requests a waiver from conducting a bioavailability/bioequivalence study for Thioridazine Hydrochloride Oral Solution (Concentrate), 100 mg/mL under the provisions of 21 CFR 320.22 (b) (3). The firm has under separate submission (ANDA# 40-125) requested for waiver of another strength (30 mg/mL) of the same drug product. Thioridazine is effective in reducing excitement, hypermotility, abnormal initiative, affective tension and agitation through its inhibitory effect on psychomotor functions. Innovator product is Mellaril^R Oral Solution (Concentrate), 100 mg/mL manufactured by Sandoz Pharmaceuticals Corporation.

FORMULATIONS: **NOT TO BE RELEASED UNDER FOI**

The comparative formulations of the test and reference products are as follows:

| <u>Ingredients</u> | <u>Amount / 1 mL</u> | |
|--|--|------------------------|
| | Test | Reference* (Sandoz) |
| Thioridazine HCl, USP | 100 mg | 100 mg |
| Alcohol, 95% |  | |
| Glycerin, USP | | |
| Methylparaben, NF | | |
| Propylparaben, NF | | |
| Sorbitol Solution 70%, USP | | |
| Sucrose | | |
|  (b)4 - Confidential Business | | |

(b)4 - Confidential
Business

Purified Water
Sodium Hydroxide
Hydrochloric Acid

pH

(b)4 -
Confidential
Business

(b)4 -
Confidential
Business

* Formulation obtained from Division of Neuropharmacological Drug Products, FDA (NOT TO BE RELEASED UNDER FOI)

1. Glycerin, propylparaben and sorbitol concentrations are lower in test compared to reference product. Methylparaben and sucrose concentrations are higher in test compared to reference product but within the potency range given in IIG for same route of administration. pH range is slightly different in two products. [USP specifications for Thioridazine Hydrochloride are: between 4.2 and 5.2, in a solution (1 in 100)]. Division of Chemistry should make a note of this and ascertain whether these differences will be of any concern for stability of the product.

2. (b)4 in test product is different from the flav used in the reference product. Composition of this flavor is not given. The firm has included certificate of analysis from its manufacturer which states that all ingredients conform to FDA regulations and are listed in the current FEMA/GRAS lists.

DEFICIENCIES:

1. Glycerin and sucrose are listed in the composition of reference product: Mellaril Oral Solution (Concentrate) 100 mg/mL of Sandoz (Physicians' Desk Reference, 1995). The firm has also included them in their list of components on page 83 and other places in the submission. However, both of these ingredients are not listed in side by side qualitative 'comparison of formulations' on page 81. The firm should clarify this.

2. The firm should provide composition of (b)4 - Confidential and provide the information demonstrating that this ingredient in the quantities used will not affect the safety of the product.

RECOMMENDATION:

The Division of Bioequivalence does not agree that the information submitted by Hi-Tech Pharmacal Co., Inc. demonstrates that Thioridazine Hydrochloride Oral Solution (Concentrate), 100 mg/mL falls under 21 CFR Section 320.22 (b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for Thioridazine Hydrochloride Oral Solution (Concentrate), 100 mg/mL is not granted.

The firm should be informed of the deficiencies.

[Redacted] /S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

[Redacted] /S/

RD INITIALED R.PATNAIK
FT INITIALED R.PATNAIK

Date

7/6/95

[Redacted] /S/

Concur:

Date

7/25/95

K
Director, Division of Bioequivalence

cc: ANDA # 40-126 (original), HFD-600 (Hare), HFD-630, HFD-655
(Patnaik, Dhariwal), Drug File, Division File

KRD/Draft 061495/40126W.D94