40027

MAR 21 1996

Promethazine HCl; Dextromethorphan HBr
6.25 mg/5 mL & 15 mg/5 mL, Syrup
ANDA # 40-027
Reviewer: S. P. Shrivastava
WP 40027W.595

Hi-Tech Pharmacal Co., Inc.
Amityville, NY
Submission Date:
May 26, 1995

Review of a Waiver Request

The firm has requested a waiver for *in vivo* bioequivalence study for its promethazine HCl/dextromethorphan HBr, 6.25 mg/5 mL & 15 mg/5 mL, respectively, under 21 CFR 320.22 (b)(3). In 1991, a waiver on this product was granted by the Division of Bioequivalence (Re: review by Shrivastava, 11/13/91), but the firm modified the formulation prior to the approval of the product.

The proposed product contains the active ingredient, promethazine HCl/dextromethorphan HBr in the same concentration as in the approved drug product, Phenergan^R with dextromethorphan, 6.25 mg/5 mL & 15 mg/5 mL (Wyeth-Ayerst, # N11265, 4/2/84). The firm has submitted a copy of the package inserts, labels, and composition of the product formulation.

Comments

1. The innovator and Hi-Tech Pharmacal, Inc. formulations are similar (Tables 1, 2).

2. The package insert and labels for the test product contain information similar to the reference product.

3. The test product is an oral solution (syrup) and contains active ingredient or therapeutic moiety in the same concentration as the drug product, Phenergan^R with dextromethorphan (Wyeth-Ayerst), that is the subject of an approved full NDA.

4. It contains inactive ingredients within the IIG limits for oral solutions (syrup).

5. The firm has met the criteria for waiver of the *in vivo* bioequivalence requirement for its promethazine HCl/dextromethorphan HBr, 6.25 mg/5 mL & 15 mg/5 mL, as per 21 CFR 320.22 (b)(3).

Recommendation

The Division of Bioequivalence agrees that the information submitted by Hi-Tech Pharmacal, Inc. demonstrates that promethazine HCl/dextromethorphan HBr, oral syrup, 6.25 mg/5 mL & 15 mg/5 mL, falls under 21 CFR, Section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for dextromethorphan.HBr, 6.25 mg/5 mL & promethazine.HCl, 15 mg/5 mL test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test syrup formulation to be bioequivalent to

Phenergan[R] with dextromethorphan, 6.25 mg/5 mL & 15 mg/5 mL, which is manufactured by Wyeth-Ayerst.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK /S/ -3/21/96

Concur: /S/ Date: 3/21/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

SPS/sps/3-20-96/40027W.595

cc: ANDA #40-027, HFD-630, HFD-600 (Hare), HFD-630, HFD-655 (Patnaik, Shrivastava), Drug File, Division File.

TABLE 1. Comparison of Reference and Test Product Formulations

ITEM	TEST PRODUCT	REFERENCE PRODUCT
Manufacturer	Hi-Tech Pharmacal, Inc.	Wyeth-Ayerst
Product name	Promethazine HCl dextromethorphan HBr	Phenergan[R] with dextromethorpahn
Active ingredient	Promethazine HCl/dextromethorphan HBr	
Dosage form	Oral syrup	
Strength	6.25 mg/5 mL & 15 mg/5 mL	
Bottle size	4 & 8 Fl oz, 1 pt 0.5 & 1 gallon	4 & 6 fl oz, 1 pt & 1 gallon
Route of adm.	Oral	
Indications	Promethazine with dextromethorphan is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.	

DIV

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-027 **SPONSOR :** Hi-Tech. C Inc.
DRUG & DOSAGE FORM : Promethazine.HCl + Dextromethorphen.Br.
STRENGTH (s) : 6.25 and 15 mg/5mL Syrup
TYPE OF STUDY: SD SDF MULT OTHER X
STUDY SITE: CLINICAL : **ANALYTICAL :**

STUDY SUMMARY :

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)				
AUC(0-T) ngxhr/ml				
AUC(0-Inf)ngxhr/ml				
Tmax hr				
Half-life hr				

① The product is an oral solution and contains active ingredients in the same conc. as the ref. Phenergan® (Wyeth-Ayerst).
② Contains inactive ingredients within the FDA limits
③ The firm modified the formulation prior to full approval of the product. Another waiver was approved by the reviewer before (11/13/91).

DISSOLUTION :
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
15		
30		
45		

Q =

PRIMARY REVIEWER : S. P. Shrivastava **BRANCH :** II

INITIAL : S.P.S **DATE :** 3/27/96

BRANCH CHIEF : **BRANCH :**

INITIAL : /S/ **DATE :** 3/27/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : [signature] **DATE :** 3/27/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : N/A **DATE :**

NOV 13 1991

Promethazine HCl; Dextromethorphan HBr
6.25 mg/5 mL & 15 mg/5 mL, Syrup
ANDA # 40-027
Reviewer: S. P. Shrivastava
WP 40027W.891

Hi-Tech Pharmacal Co., Inc.
Amityville, NY
Submission Date:
August 29, 1991

Review of a Waiver Request

The firm has requested a waiver for *in vivo* bioequivalence study for its promethazine HCl/dextromethorphan HBr, 6.25 mg/5 mL & 15 mg/5 mL, respectively, under 21 CFR 320.22 (b)(5).

The proposed product contains the active ingredient, promethazine HCl/dextromethorphan HBr in the same concentration as in the approved drug product, Phenergan^{R} with dextromethorphan, 6.25 mg/5 mL & 15 mg/5 mL (Wyeth-Ayerst, # H11265-002). The firm has submitted a copy of the package inserts, labels, and composition of the product formulation.

Comment

1. The compositions of the innovator and Hi-Tech Pharmacal, Inc. formulations are identical (Table 1).

2. The package insert and labels for the test product contain information similar to the reference product.

3. The test product is an oral solution (syrup) and contains active ingredient or therapeutic moiety in the same concentration as the drug product, Phenergan^{R} with dextromethorphan (Wyeth-Ayerst), that is the subject of an approved full NDA. The drug product is coded AA in the Therapeutic Equivalence List.

4. It contains no inactive ingredients that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

5. The firm has met the criteria for waiver of the *in vivo* bioequivalence requirement for its promethazine HCl/dextromethorphan HBr, 6.25 mg/5 mL & 15 mg/5 mL, as per 21 CFR 320.22 (b)(5).

Recommendation

The Division of Bioequivalence agrees that the information submitted by Hi-Tech Pharmacal, Inc. demonstrates that promethazine HCl/dextromethorphan HBr, oral syrup, 6.25 mg/5 mL & 15 mg/5 mL falls under 21 CFR, Section 320.22(b)(5) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the 6.25 mg/5 mL & 15 mg/5 mL test product

is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test syrup formulation to be bioequivalent to Phenergan® with dextromethorphan, 6.25 mg/5 mL & 15 mg/5 mL, manufactured by Wyeth-Ayerst.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK /S/

Concur: /S/ Date: 11/7/91

Ramakant Mhatre, Ph.D.
Acting Deputy Director
Division of Bioequivalence

SPS/sps/10-24-91/40027W.891

cc: ANDA #40-027, HFD-630, HFD-604 (Hare), HFC-130 (JAllen), HFD-655 (Patnaik, Shrivastava), HFD-340, Drug File.

TABLE 1. Comparison of Reference and Test Product Formulations

ITEM	TEST PRODUCT	REFERENCE PRODUCT
Manufacturer	Hi-Tech Pharmacal, Inc.	Wyeth-Ayerst
Product name	Promethazine HCl dextromethorphan HBr	Phenergan[R] with dextromethorpahn
Active ingredient	Promethazine HCl/dextromethorphan HBr	
Dosage form	Oral syrup	Oral syrup
Strength	6.25 mg/5 mL & 15 mg/5 mL	
Bottle size	4 & 8 Fl oz, 1 pt 0.5 & 1 gallon	4 & 6 fl oz, 1 pt & 1 gallon
Route of adm.	Oral	Oral
Indications	Promethazine with dextromethorphan is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.	

D.J

ANDA 40-027

APR - 3 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 submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Promethazine Hydrochloride and Dextromethorpan Hydrobromide Syrup, 6.25 mg/5 mL and 15 mg/5 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