CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40372

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-372 SPONSOR : Abbott Laboratories

DRUG AND DOSAGE FORM : **Promethazine Hydrochloride Injection, USP**

STRENGTH(S) : **25 mg/mL, 1 mL fill Carpujet® and 50 mg/mL, 1 mL fill Carpujet®**

TYPES OF STUDIES : Waiver request

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : The formulation is acceptable under 21 CFR 314.94 (a)(9)(iii). The proposed product is bioequivalent to the RLD under 21 CFR 320.24(b)(6).

DISSOLUTION : N/A

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: Carol Y. Kim BRANCH : III

INITIAL : /S/ for T DATE : 7/21/99

TEAM LEADER: Barbara M. Davit BRANCH : III

INITIAL : BMD DATE : 7/21/99

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

INITIAL : [signature] DATE : 8/2/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-372 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Promethazine Hydrochloride Injection, 25 mg/ml and 50 mg/ml

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Promethazine Hydrochloride Injection, USP
25 mg/ml, 1ml fill Carpuject[R]
50 mg/ml, 1 ml fill Carpuject[R]
ANDA # 40-372
Reviewer: Carol Y. Kim
V:\firmsam\abbott\ltrs&rev\40372w.799

Abbott Laboratories
Abbott Park, IL
Submission Date:
~~July 6, 1999~~
MAY 28, 1999

REVIEW OF TWO WAIVER REQUESTS

I. Background

1. The firm has requested waivers of *in vivo* bioequivalence study requirements for its proposed products, Promethazine Hydrochloride Injection, 25 mg/ml and 50 mg/ml, 1 ml fill Carpuject®. The reference listed product is Phenergan[R] (Promethazine HCl) Injection, 25 mg/ml and 50 mg/ml, 1 ml fill Tubex® Sterile Cartridge-Needle Unit, manufatured by Wyeth-Ayerst Company.

2. Tubex® is a proprietary name for Wyeth-Ayerst Company's injectable delivery system, and Carpuject® is Abbott's injectable delivery system. They both deliver the same amount of ready-to-use solution, 1 ml, through pre-filled syringe.

3. Promethazine HCl Injection is a ready-to-use solution for injection indicated for amelioration of allergic reactions to blood or plasma, in treatment of motion sickness, in prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.

4. The reference drug product, Phenergan[R] (Promethazine HCl) Injection, is to be administered by either the intravenous or intramuscular route. The same routes of administration apply for the proposed product, Promethazine HCl Injection.

II. Formulation Comparison

The test and reference formulations are compared as shown below:

Ingredients	*Phenergan[R] (Promethazine HCl) Injection 25 mg/ml, (per ml)	Ingredients	Abbott's Promethazine HCl Injection, USP, 25 mg/ml, (per ml)
Promethazine Hydrochloride	25 mg	Promethazine Hydrochloride, USP	25 mg
Edetate Disodium	0.1 mg	Edetate Disodium, USP (100% basis)	0.1 mg
Calcium Chloride	0.04 mg	Calcium Chloride, USP	
Sodium Metabisulfite	0.25 mg	Monothioglycerol, NF	5 mg
Phenol	5 mg	Phenol, USP	5 mg
Sodium Acetate	Adjust pH 4-5.5	Sodium Acetate, USP (Trihydrate)	Adjust pH to 4.9
Glacial Acetic Acid	Adjust pH 4-5.5	Glacial Acetic Acid, USP	Adjust pH to 4.9
Water for Injection, USP (q.s.)	QS to 1 ml	Water for Injection, USP (q.s.)	QS to 1 ml

Ingredients	*Phenergan^R (Promethazine HCl) Injection 50 mg/ml, per ml	Ingredients	Abbott's Promethazine HCl Injection, USP, 50 mg/ml (per ml)
Promethazine Hydrochloride	50 mg	Promethazine Hydrochloride, USP	50 mg
Edetate Disodium	0.1 mg	Edetate Disodium, USP (100% basis)	0.1 mg
Calcium Chloride	0.04 mg	Calcium Chloride, USP	
Sodium Metabisulfite	0.25 mg	Monothioglycerol, NF	5 mg
Phenol	5 mg	Phenol, USP	5 mg
Sodium Acetate	Adjust pH 4-5.5	Sodium Acetate, USP (Trihydrate)	Adjust pH to 4.9
Glacial Acetic Acid	Adjust pH 4-5.5	Glacial Acetic Acid, USP	Adjust pH to 4.9
Water for Injection, USP (q.s.)	QS to 1 ml	Water for Injection, USP (q.s.)	QS to 1 ml

*From PDR 1999, p. 3356

[1]Equivalent to 0.04 mg calcium chloride anhydrous

III. Comments

1. The test products, Promethazine Hydrochloride Injection, 25 mg/ml and 50 mg/ml, contain the same active ingredients in the same concentrations and dosage forms as the reference products, Phenergan^R (Promethazine HCl) Injection, 25 mg/ml and 50 mg/ml.

2. Abbott's formulation for Promethazine HCl Injections, 25 mg/ml and 50 mg/ml, contains Monothioglycerol NF at 5 mg/ml instead of Sodium Metabisulfite which is presently used in Phenergan^R (Promethazine HCl), 25 mg/ml and 50 mg/ml, Injections. Phenergan^R was initially approved with Monothioglycerol at 5 mg/ml as a preservative, but the innovator recently substituted Sodium Metabisulfite for Monothioglycerol. (PDR 1999, p. 3356)

3. The proposed product is acceptable under 21 CFR 314.94 (a) (9) (iii), which states that an applicant may seek the approval of the drug product that differs from the RLD in preservatives, buffers, or anti-oxidants provided that the applicant identifies and characterize the differences and provide information demonstrating that the differences did not effect the safety of the proposed drug product. The proposed product is bioquivalent to the RLD under 21 CFR 320.24 (b) (6).

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories demonstrates that Promethazine HCl, 25 mg/ml and 50 mg/ml, Injections are acceptable under 21 CFR section 320.24 (b) (6) and 21 CFR section 314.94 (a) (9) (iii) of the Bioavailability/Bioequivalence Regulations. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulations to be bioequivalent to

Phenergan[R] (Promethazine HCl), 25 mg/ml and 50 mg/ml, Injections, manufactured by Wyeth-Ayerst Company.

The firm should be informed of the recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT GMD 7/21/99
FT INITIALLED BY BDAVIT /S/ Date: 7/21/99

Concur. /S/ Date: 8/2/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence