CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40372

CORRESPONDENCE

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

May 22, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Acting Director

VIA FAX (301) 594-0180
(paper copy via mail)

Re: ANDA 40-372 Promethazine Hydrochloride Injection, 25 mg/mL and 50 mg/mL (Carpuject®)

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above referenced abbreviated new drug application for the drug product. This is in response to the telephone conversation held between Dr. Paul Schwartz and Ms. Elaine Hu, FDA, and Drs. Thomas Willer and Jessie Lee, Abbott Laboratories, on May 19, 2000 regarding the finished product specifications. The Agency was requesting the change of the specification for "Other Requirements" from "Meets USP 23 requirements under Injections <1> (specifically for Sterility <71> and Volume in Container <1>" to "Meets the Current USP Requirements under Injections <1>".

We responded to the Agency's request for the revision of the finished product specifications for "Other Requirements" in the original ANDA, Section XVI. 3. c., Page 722, on May 19, 2000. After a thorough review of the amendment, we discovered the same issue shown in other sections of the submission. We have revised the finished product specifications of these sections (Section XV.2. and XVI.3.c.) to be consistent with the Agency's comment. In addition, we have also revised the specification for the Description Test and the footnote #1 under Section XVII.1.C. The revised specifications for the finished product and stability are provided in Exhibit I and Exhibit II.

We trust that this submission is complete. If there are any further questions, please contact me.

Sincerely,
ABBOTT LABORATORIES

Jessie Y. Lee

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-5513
Fax: (847) 938-7867
e-Mail: LEEJ@hpd.abbott.com

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ABBOTT

Hospital Products Division
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Abbott Park, Illinois 60064-6157

May 19, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

N/FA

ATTENTION: Gary J. Buehler
Acting Director

VIA FAX (301) 594-0180
(paper copy via mail)

Re: ANDA 40-372 Promethazine Hydrochloride Injection, 25 mg/mL and 50 mg/mL (Carpuject®)

TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above referenced abbreviated new drug application for the drug product. This is in response to the telephone conversation held between Dr. Paul Schwartz and Ms. Elaine Hu, FDA, and Drs. Thomas Willer and Jessie Lee, Abbott Laboratories, on May 19, 2000 regarding the finished product specifications under Other Requirements in the original ANDA, Section XVI. 3. c., Page 722. The Agency was requesting the change of this section from "Meets USP 23 requirements under Injections <1>(specifically for Sterility <71> and Volume in Container <1>" to "Meets the Current USP Requirements under Injections <1>".

We have revised the finished product specifications per Agency's comment. The revised document is provided in Exhibit I.

We trust that this submission is complete. If there are any further questions, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

Jessie Y. Lee

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
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ABBOTT

Hospital Products Division
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Abbott Park, Illinois 60064-6157

April 14, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA UNIT ASSIGNMENT
N/FA

ATTENTION: Gary J. Buehler
Acting Director

Re: ANDA 40-372 Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL (Carpuject®)

RESPONSE TO MICROBIOLOGY DEFICIENCIES

Abbott Laboratories hereby amends the above referenced abbreviated new drug application for the drug product submitted May 28, 1999 and January 18, 2000. We are responding to the Agency's action letter dated March 24, 2000. The Agency made the following comments:

A. Microbiology Deficiencies:

COMMENT: "1. **With regard to the of filling equipment, please describe how the revalidation load for compares to production sterilization loads for and filling equipment."**

RESPONSE: We note that the loading pattern, which is the loading pattern used for the consists of common equipment items which may be used for multiple filling lines (i.e. Since sterilization of filling equipment was qualified by challenging the worst case load configuration, the loading pattern was chosen because the filling pump setup represents more mass than the filling pump setup, which has similar material construction (i.e. stainless steel and tubing).

COMMENT: "2. **Please submit sterilization validation data for if they are used to sterilize plungers and cartridges for the drug product."**

RESPONSE: Exhibit I contains the sterilization validation data for the com 231.

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Exhibit II contains the sterilization validation data for the components

COMMENT: "3. **Please submit validation data for the sterilization/depyrogenation of glass cartridges by**

RESPONSE: Exhibit III contains the validation data for the sterilization/depyrogenation of glass cartridges by

B. **In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:**

COMMENT: **"The bulk solution bioburden was highly variable during the media fill runs; you may want to consider implementing additional controls to reduce the variability of bioburden."**

RESPONSE: We note and acknowledge that the bulk solution bioburden was highly variable during the media fill runs. However, we note that our process for manufacture of bulk solution requires,

We trust that this submission is complete. If you require any clarification or further information, please telephone me at (847) 937-4772.

Sincerely,

ABBOTT LABORATORIES

Kenneth Oh 4/14/00

Kenneth Oh
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-4772
FAX: (847) 938-7867

ABBOTT

Hospital Products Division
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NDA DRUG AMENDMENT

January 18, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Douglas Sporn
Director

ELECTRONIC SUBMISSION
ENCLOSED

Re: ANDA 40-372 Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL (Carpuject®)

RESPONSE TO CHEMISTRY AND LABELING DEFICIENCIES

FAX AMENDMENT

Abbott Laboratories hereby amends the above referenced abbreviated new drug application for the drug product submitted May 28, 1999. We are responding to the Agency's action letter dated December 23, 1999. The Agency made the following comments:

A. Chemistry Deficiencies:

COMMENT: "1. **Please submit a COA for the drug substance from the drug substance manufacturer that is legible."**

RESPONSE: Exhibit I contains a legible COA from the drug substance manufacturer for the drug substance.

COMMENT: "2. **Please set a specification and perform melting point testing for the drug substance."**

RESPONSE: Exhibit II contains the revised drug substance specification to include the test and specification for melting range.

Exhibit III contains the revised in-house COA for the drug substance Lot # 9719902, which used in the manufacture of the exhibit batches, to include the test result for melting range.

COMMENT: "3. **Please set a specification for the density in-process test."**

RESPONSE: Exhibit IV contains the revised in-process specification to include an established specification for the density test.

COMMENT: "4. **At each 3 month accelerated stability test point the degradation/related compounds results are "none detected", whereas in the previous months (initial, 1 and 2 months) results were reported. Please explain."**

RESPONSE: Upon review of the stability data we have concluded that the difference in profiles for degradation products/related compounds at various test stations, especially at 3 month test point, is attributed to the sensitivity of the method and the low levels in which the results were observed (close to limit of detection of % and below the limit of quantitation of %). In addition, based on the review of the stability data, we have updated the 3 month test point to include the low levels of degradants/related compounds previously not reported. Please refer to Exhibit V.

COMMENT: "**In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:**

1. **The firms referenced in your application must be in compliance with CGMP at the time of approval."**

RESPONSE: We note and acknowledge that the firms referenced in the application must be in compliance with CGMP at the time of approval.

COMMENT: "2. **The microbiological portion of your application is under review. You will be notified of the findings."**

RESPONSE: We note and acknowledge that the microbiological portion of the application is under review and we will be notified of the findings under separate cover.

COMMENT: "3. **Please submit all updated stability data."**

RESPONSE: Exhibit V contains updated 12 months controlled room temperature stability data for the exhibit batches.

Labeling Deficiencies:

COMMENT: "1. **CONTAINER - (25 mg/mL & 50 mg/mL Carpuject)**
Satisfactory in final print as of May 28, 1999 submission.

2. **CARTON - 10's**
Satisfactory in final print as of May 28, 1999 submission.

3. **INSERT**
   a. **Title**
   b. **We encourage you to include "Rx only" as part of this section.**

WARNINGS
Use in Geriatric Patients (APPROXIMATELY 60 YEARS OR OLDER)

HOW SUPPLIED

"Protect from light" [Use bold lettering as does the innovator]

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, It may necessary to further revise your labeling subsequent to approved changes for the referenced listed drug. We suggest that you routinely monitor the following website for any approved changes-http:www.fda.gov/cder/ogd/rid/labeling_review_branch.html

To facilitate *review* of your next submission, and in accordance with 21 CFR 314,94(e)(8)iv), please provide a· side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

RESPONSE We made the requested changes to the package insert with one exception. Under provisions of FDAMA '97 inclusion of the designation "Rx Only" is not mandatory for package insert. We have not included it on this insert labeling. Please see Exhibit VI for the annotated package insert. Please see Exhibit VII for twenty copies of final printed package inserts.

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

Response: No response required.

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drug (OGD) electronic submission program using Entry Validation Application (EVA). A one page printout of the EVA log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

We trust that this submission is complete. If you require any clarification or further information, please telephone me at (847) 937-6845.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
FAX: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

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ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

July 2, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS,
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Mr. Nasser Mahmud

Via FAX 301-594-1174
(Paper Copy Sent via Mail)

Re: ANDA 40-372 Promethazine HCl Injection, USP, 25 mg/mL (1 mL fill in 2 mL Carpuject®) and 50 mg/mL (1 mL fill in 2 mL Carpuject®)

TELEPHONE CORRESPONDENCE

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the subject drug product submitted May 28, 1999. We are responding to a telephone request on July 1, 1999 from Mr. Nasser Mahmud and Mr. Pares Patel, OGD, to Dr. Thomas Willer, Abbott Laboratories concerning this application.

The Agency noted that the established name listed on FDA 356h form for the drug product did not include the "USP" designation. Exhibit I contains the revised 356h form to include the "USP" designation for the drug product name.

In addition, the agency requested clarification regarding the batch accountability for Lot # PD8-396B and Lot # PD8-397B which are referenced on page 263 and page 356, respectively, of the original submission. We hereby confirm that Lot # PD8-396B (for plunger and 8-I seal) was filled from the parent lot # PD8-396A and Lot # PD8-397B (for plunger and 8-I seal) was filled from the parent lot # PD8-397A. These two lots were also placed on stability. However, since we do not intend to utilize the rubber components, Lot # PD8-396B and Lot # PD8-397B were not included in the ANDA submission. In addition, we note that the accountability and yield analysis for Lot # PD8-396B are included on pages 264-266 of the original submission, and the accountability and yield analysis for Lot # PD8-397B are included on pages 358-360 of the original submission. For your convenience, a copy of pages 264-266 and pages 358-360 is provided in Exhibit II.

ABBOTT

Hospital Products Division
Abbott Laboratories
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May 28, 1999

505(j)(2)(A)
P.M. Fahey

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Douglas Sporn
Director

ELECTRONIC SUBMISSION ENCLOSED

Re: Promethazine Hydrochloride Injection, USP, 25 mg/mL and 50 mg/mL (Carpuject®)
Original Abbreviated New Drug Application

Abbott Laboratories hereby submits an Abbreviated New Drug Application for Promethazine Hydrochloride Injection, USP, 25 mg/mL (1 mL fill in 2 mL Carpuject®) and 50 mg/mL (1 mL fill in 2 mL Carpuject®), in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act. The subject drug is a prescription drug and not an over-the-counter drug.

Promethazine Hydrochloride Injection, USP, is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 19th Edition, page 3-280. A copy appears in Section II.

The active ingredient, indications (applicable to the injection), route of administration, dosage form, and strength for Promethazine Hydrochloride Injection, USP, are the same as those of the innovator's product, Phenergan® Injection, sponsored by Wyeth Laboratories Inc., a Wyeth-Ayerst Company. Comparative information is contained in Section IV.

The labeling is the same in content as that of the reference drug, Phenergan® Injection, except for changes that are necessary due to a change in manufacturer. A copy of the innovator's package insert is provided in Section V.

The first three production batches of Promethazine Hydrochloride Injection, USP, 25 mg/mL (1 mL fill in 2 mL Carpuject®) and 50 mg/mL (1 mL fill in 2 mL Carpuject®), will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Our complete stability protocol and post-approval commitments are contained in Section XVII.

For the convenience of the Agency, documentation for Sterilization Process Validation is contained in a separate volume with a dedicated table of contents.

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drugs (OGDs) electronic submission program using Entry Validation Application (EVA). A one-page printout of the EVA log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

This original ANDA applies to the manufacturing facility in McPherson, Kansas. The establishment registration number is 1925262. Abbott Laboratories hereby certify that we have sent a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call me at (847) 937-6845.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

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Associate Director, Regulatory Affairs
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Attachment

ABBOTT

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May 18, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Douglas Sporn
Director

Re: Promethazine Hydrochloride Injection, USP, 25 mg/mL and 50 mg/mL (Carpuject®)
Original Submission: Patent Certification and Exclusivity Statement

Abbott Laboratories hereby certify under § 505(j)(a)(A)(vii) of the Federal Food, Drug, and Cosmetic Act as amended in Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 that, to the best of its knowledge, all patents filed by the holder of any approved application covering Promethazine Hydrochloride Injection, USP, 25 mg/mL and 50 mg/mL, have expired.

Further, to the best of its knowledge, there is no exclusivity period in force for the above referenced drug product.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

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