CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-428

Generic Name: Promethazine Hydrochloride Suppositories USP, 25 mg

Sponsor: G & W Laboratories, Inc.

Approval Date: February 5, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-428

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ANDA 40-428

FEB 5 2002

G & W Laboratories, Inc.
Attention: Hindy Schiff
111 Coolidge Street
South Plainfield, NJ 07080

Dear Madam:

This is in reference to your abbreviated new drug application dated December 19, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Promethazine **Hydrochloride Suppositories USP, 25 mg.**

Reference is also made to your amendments dated August 22, September 14, October 30, November 29, December 6, and December 21, 2001; and January 8, 2002.

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 your Promethazine Hydrochloride Suppositories USP, 25 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Phenergan® Suppositories, 25 mg, of Wyeth Ayerst Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, 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 and 314.98. 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 that 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-40). Please do not use Form FD-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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

2/5/02

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-428

Final Printed Labeling

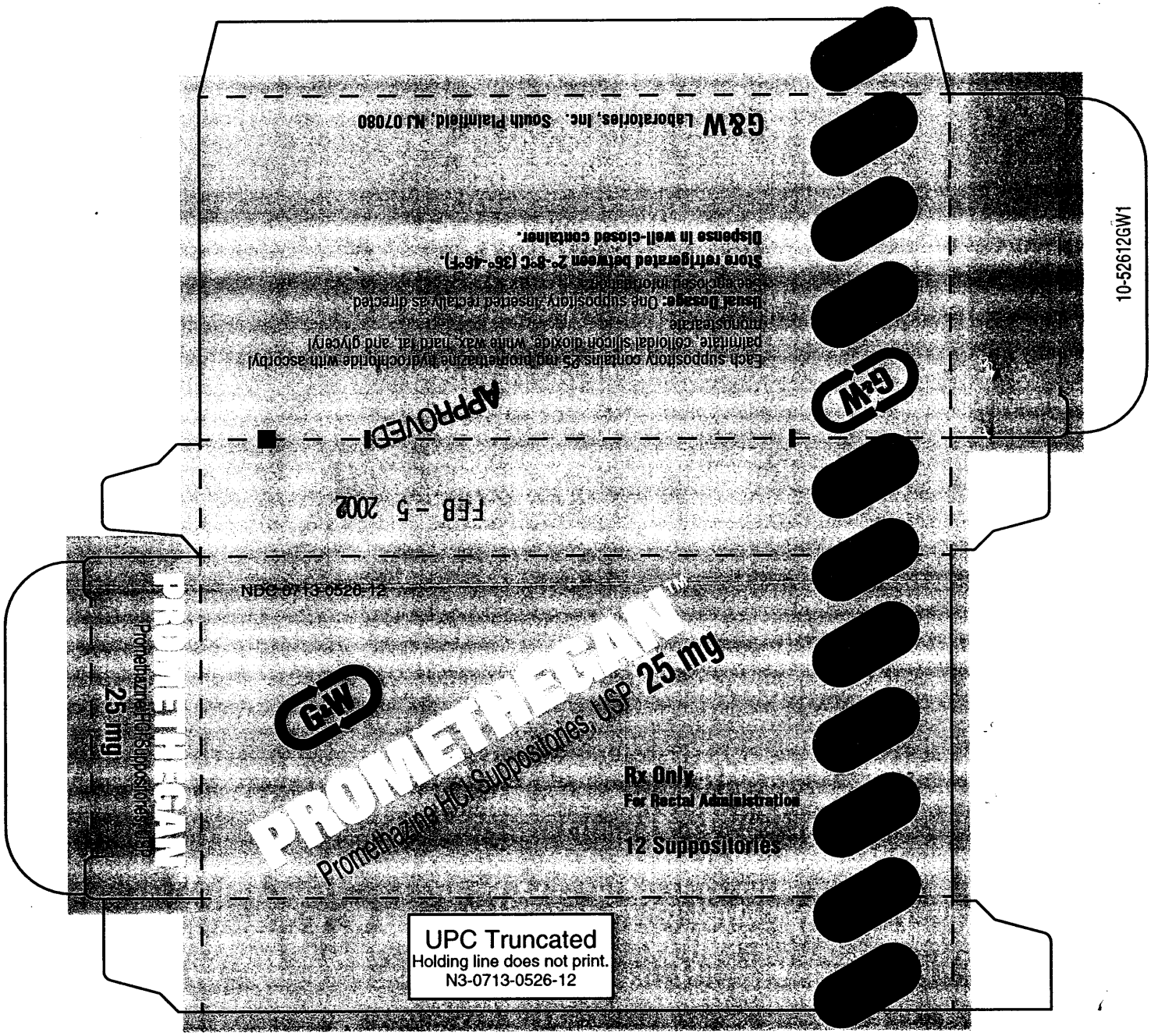


DIAGRAM 1812
2 9/32 X 25/32 X 5
13212

G&W LABORATORIES, INC.	COLORS Note: PMS Swatch on proof does not represent exact color.	PMS 406 / PMS 4645 / Black	AUTHORIZED SIGNATURE DATE	PROOF APPROVED / REPROOF REQUIRED

PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES, USP

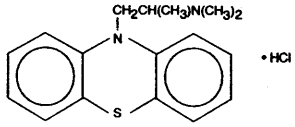
Rx Only

DESCRIPTION

Each rectal suppository contains 25 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, hard fat, and glyceryl monostearate.

Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S{\cdot}HCl$ and its molecular weight is 320.88.

Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10*H*-Phenothiazine, 10-ethanamine, *N,N,* α-trimethyl-, monohydrochloride, (±)- with the following structural formula:



Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

CLINICAL PHARMACOLOGY

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.

Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosage, promethazine produces no significant effects on the cardiovascular system.

Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethyl-promethazine are the predominant metabolites appearing in the urine.

INDICATIONS AND USAGE

Promethazine HCl Suppositories are useful for:

Perennial and seasonal allergic rhinitis.
Vasomotor rhinitis.
Allergic conjunctivitis due to inhalant allergens and foods.
Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.
Amelioration of allergic reactions to blood or plasma.
Dermographism.
Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.
Preoperative, postoperative, or obstetric sedation.
Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
Therapy adjunctive to meperidine or other analgesics for control of postoperative pain.
Sedation in both children and adults, as well as relief of apprehension and production of light sleep from which the patient can be easily aroused.
Active and prophylactic treatment of motion sickness.
Antiemetic therapy in postoperative patients.

CONTRAINDICATIONS

Promethazine is contraindicated in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

WARNINGS

Promethazine may cause marked drowsiness. Ambulatory patients should be cautioned against such activities as driving or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.

The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics or local anesthetics which may also affect seizure threshold.

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.

Administration of promethazine has been associated with reported cholestatic jaundice.

Precautions

GENERAL

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

INFORMATION FOR PATIENTS

Promethazine HCl Suppositories may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from promethazine hydrochloride therapy. Children should be supervised to avoid potential harm in bike riding or other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

DRUG INTERACTIONS

The sedative action of promethazine is additive to the sedative effects of other central nervous system depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

DRUG/LABORATORY TEST INTERACTIONS

The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

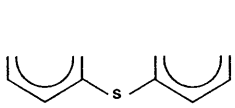
Pregnancy Tests

Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test

An increase in blood glucose has been reported in patients receiving promethazine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY



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FEB - 5 2002

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Amelioration of allergic reactions to blood or plasma.
Dermographism.

APPROVED

Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.
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Glucose Tolerance Test

An increase in blood glucose has been reported in patients receiving promethazine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to assess the carcinogenic potential pf promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

PREGNANCY

Teratogenic Effects - Pregnancy Category C

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women. Promethazine HCl Suppositories should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Promethazine taken within two weeks of delivery may inhibit platelet aggregation in the newborn.

LABOR AND DELIVERY

Promethazine HCl Suppositories, in appropriate dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See **"Indications and Usage"** and **"Dosage and Administration."**)

See also *"Nonteratogenic Effects."*

NURSING MOTHERS

It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.

PEDIATRIC USE

This product should not be used in children under 2 years of age because safety for such use has not been established.

Adverse Reactions

Nervous System — Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
Cardiovascular — Increased or decreased blood pressure.
Dermatologic — Rash, rarely photosensitivity.
Hematologic — Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).
Gastrointestinal — Nausea and vomiting.

Overdosage

Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single dosages of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms-dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms, may occur.

TREATMENT

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine are not reversed by naloxone. Avoid analeptics which may cause convulsions.

Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure.

Limited experience with dialysis indicates that it is not helpful.

Dosage and Administration

ALLERGY

The average dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Children tolerate this product well. Single 25 mg doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The administration of promethazine hydrochloride in 25 mg doses will control minor transfusion reactions of an allergic nature.

MOTION SICKNESS

The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, Promethazine HCl Rectal Suppositories, 12.5 to 25 mg, twice daily, may be administered.

NAUSEA AND VOMITING

The average effective dose of promethazine hydrochloride for the active therapy of nausea and vomiting in children or adults is 25 mg. 12.5 to 25 mg doses may be repeated, as necessary, at 4 to 6 hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg per pound of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4 to 6 hour intervals, as necessary.

SEDATION

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg promethazine hydrochloride by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.

PRE- AND POSTOPERATIVE USE

Promethazine HCl in 12.5 to 25 mg doses for children and 50 mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication children require doses of 0.5 mg per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug.

Usual adult dosage is 50 mg promethazine hydrochloride with an equal amount of meperidine and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5 to 25 mg in children and 25 to 50 mg doses in adults.

Promethazine HCl Rectal Suppositories are not recommended for children under 2 years of age.

How Supplied

Promethazine HCl Rectal Suppositories are available in boxes of 12 as follows:

25 mg, white, bullet-shaped suppository wrapped in silver foil. NDC 0713-0526-12

Store refrigerated between 2°-8°C (36°-46°F).

PEDIATRIC USE

This product should not be used in children under 2 years of age because safety for such use has not been established.

Adverse Reactions

Nervous System — Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
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Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine are not reversed by naloxone. Avoid analeptics which may cause convulsions.

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25 mg, white, bullet-shaped suppository wrapped in silver foil. NDC 0713-0526-12

Store refrigerated between 2°-8°C (36°-46°F).

Dispense in well-closed container.

Manufactured by:
G & W Laboratories, Inc., 111 Coolidge Street, South Plainfield, N.J. 07080

8-0526GW1
Issued 3/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-428

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 40-428 **[Promethazine Hydrochloride Suppositories]**

3. **NAME AND ADDRESS OF APPLICANT**

G & W Laboratories, Inc.
Attention: Hindy Schiff
111 Coolidge Street
South Plainfield, NJ 07080
Tel: (908) 753-2000 FAX: (908) 753-9264

4. **LEGAL BASIS FOR SUBMISSION**

The basis of the ANDA is the approved listed drug, Phenergan® Suppositories, containing 25 mg promethazine Hydrochloride (NDA #10-926). According to information published in the Orange Book, Phenergan® Suppositories are not entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Act as a new chemical entity.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/AS

7. **NONPROPRIETARY NAME**

Promethazine Hydrochloride Suppositories USP, 25 mg

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

G & W

12/19/00	ANDA submission (received on 12/20/00)
01/22/01	Amendment (Re:a variety of information)

FDA

01/12/01	Request information (via teleconference)
02/01/01	Acknowledgment letter (acceptable for filing 12/20/00)

10. **PHARMACOLOGICAL CATEGORY** Antihistamine, antiemetic

11. **Rx or OTC** Rx

12. **RELATED IND/NDA/DMF(s)**

NDA #10-926, Phenergan® Suppositories (Wyeth-Ayerst, approved 01/01/1982). As of this review, OGD has approved the following ANDAs of Promethazine HCl Suppositories:

ANDA#	Firm	Strength	Date of Approval
84-901	Polymedica	25 mg	10/05/81
84-902	Polymedica	50 mg	10/05/81
87-165	G and W Lab	50 mg	08/14/87

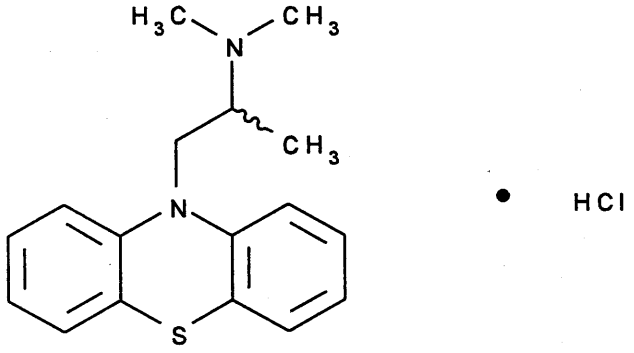
13. **DOSAGE FORM** Suppositories (rectal administration)

14. **STRENGTH** 25 mg

15. **CHEMICAL NAME AND STRUCTURE**

Promethazine Hydrochloride USP

$C_{17}H_{20}N_2S.HCl$; M.W. = 320.88



(±)-10-[2-(Dimethylamino)propyl]phenothiazine monohydrochloride.
CAS [58-33-3]

16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**

Drug substance and drug product are listed in the USP 24. Method validation by FDA is not required. Type II DMF of the drug substance is adequate as of this review. There are CMC deficiencies.

Bioequivalence review is pending. Labeling review is pending.

Acceptable EER is pending.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Not Approvable (MINOR AMENDMENT)

19. **REVIEWER:**
Shing H. Liu, Ph.D.

DATE COMPLETED:
05/09/01
Revised on 05/24/01
2nd revision: 06/04/01

Redacted 18

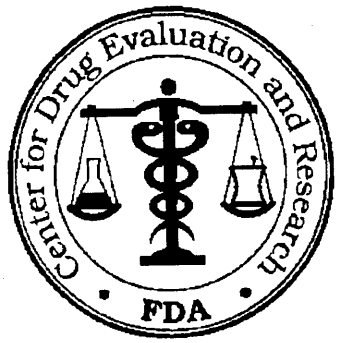
pages of trade secret and /or confidential commercial information

FAX AMENDMENT

ANDA 40-428

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV 20 2001



TO: APPLICANT: G & W Laboratories, Inc. TEL: 908-753-2000

ATTN: Hindy Schiff FAX: 908-753-9264

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 19, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Promethazine Hydrochloride Suppositories USP, 25 mg.

Reference is also made to your amendment(s) dated: July 13, 2001.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:
CMC comments provided.

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 40-428 **[Promethazine Hydrochloride Suppositories]**

3. **NAME AND ADDRESS OF APPLICANT**
G & W Laboratories, Inc.
Attention: Hindy Schiff
111 Coolidge Street
South Plainfield, NJ 07080
Tel: (908) 753-2000 FAX: (908) 753-9264

4. **LEGAL BASIS FOR SUBMISSION**
The basis of the ANDA is the approved listed drug, Phenergan® Suppositories, containing 25 mg promethazine Hydrochloride (NDA #10-926). According to information published in the Orange Book, Phenergan® Suppositories are not entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Act as a new chemical entity.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/AS

7. **NONPROPRIETARY NAME**
Promethazine Hydrochloride Suppositories USP, 25 mg

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
* denotes the amendment(s) reviewed in this chemistry review

G & W

12/19/00		ANDA submission (received on 12/20/00)
01/22/01		Amendment (Re:a variety of information)
06/18/01	*	Telephone amendment (bio issue)
07/13/01	*	Amendment (response to CMC NA letter of 06/05/01)

FDA

01/12/01	Request information (via teleconference)
02/01/01	Acknowledgment letter (acceptable for filing 12/20/00)
06/05/01	NA letter (MINOR) (based on chemistry review #1)

10. **PHARMACOLOGICAL CATEGORY** Antihistamine, antiemetic

11. **Rx or OTC** Rx

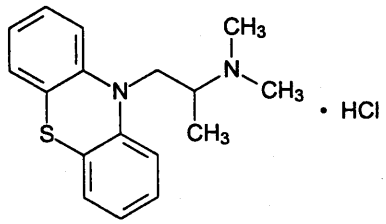
12. **RELATED IND/NDA/DMF(s)**
NDA #10-926, Phenergan® Suppositories (Wyeth-Ayerst, approved 01/01/1982). As of this review, OGD has approved the following ANDAs of Promethazine HCl Suppositories:

ANDA#	Firm	Strength	Date of Approval
84-901	Polymedica	25 mg	10/05/81
84-902	Polymedica	50 mg	10/05/81
87-165	G and W Lab	50 mg	08/14/87

13. **DOSAGE FORM** Suppositories (rectal administration)

14. **STRENGTH** 25 mg

15. **CHEMICAL NAME AND STRUCTURE**
Promethazine Hydrochloride. 10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)-.$C_{17}H_{20}N_2S$•HCl. 320.89. 58-33-3. Anti-emetic, antihistaminic.



16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**
Drug substance and drug product are listed in the USP 24. Method validation by FDA is not required. Type II DMF of the drug substance is adequate as of this review. Some CMC issues remain.

Bioequivalence review is pending. Labeling review is pending.

Acceptable EER is pending.

18. **CONCLUSIONS AND RECOMMENDATIONS**
Not Approvable

19. **REVIEWER:** Shing H. Liu, Ph.D. **DATE COMPLETED:** 08/29/01

APPEARS THIS WAY
ON ORIGINAL

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MINOR AMENDMENT

ANDA 40-428

JUN - 5 2001

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: G & W Laboratories, Inc.

TEL: 908-753-2000

ATTN: Hindy Schiff

FAX: 908-753-9264

FROM: Timothy Ames

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 19, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Promethazine Hydrochloride Suppositories USP, 25 mg.

Reference is also made to your amendment(s) dated: January 22, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: CMC comments included.

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 40-428 **[Promethazine Hydrochloride Suppositories]**

3. **NAME AND ADDRESS OF APPLICANT**

G & W Laboratories, Inc.
Attention: Hindy Schiff
111 Coolidge Street
South Plainfield, NJ 07080
Tel: (908) 753-2000 FAX: (908) 753-9264

4. **LEGAL BASIS FOR SUBMISSION**

The basis of the ANDA is the approved listed drug, Phenergan® Suppositories, containing 25 mg promethazine Hydrochloride (NDA #10-926). According to information published in the Orange Book, Phenergan® Suppositories are not entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Act as a new chemical entity.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/AS

7. **NONPROPRIETARY NAME**

Promethazine Hydrochloride Suppositories USP, 25 mg

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

* denotes the amendment(s) reviewed in this chemistry review

G & W

12/19/00	ANDA submission (received on 12/20/00)
01/22/01	Amendment (Re:a variety of information)
06/18/01	Telephone amendment (bio issue)
07/13/01	Amendment (response to CMC NA letter of 06/05/01)
11/29/01	*Fax amendment (response to CMC NA letter of 11/20/01)
11/30/01	*Fax amendment (correction of typo error in 11/29/01 amendment)
12/06/01	*Telephone amendment
12/21/01	*Bio amendment
01/07/02	*Bio amendment
01/08/02	*CMC telephone amendment

FDA

01/12/01	Request information (via teleconference)
02/01/01	Acknowledgment letter (acceptable for filing 12/20/00)
06/05/01	NA letter (MINOR) (based on chemistry review #1)
11/20/01	NA letter (MINOR) (based on chemistry review #2)
12/06/01	Telephone CMC amendment request
12/14/01	Bioequivalence Division faxed a letter

10. **PHARMACOLOGICAL CATEGORY** Antihistamine, antiemetic

11. **Rx or OTC** Rx

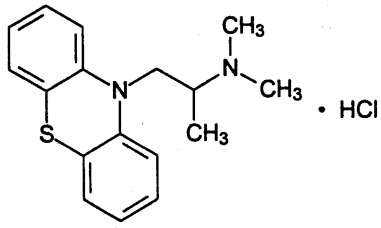
12. **RELATED IND/NDA/DMF(s)**
NDA #10-926, Phenergan® Suppositories (Wyeth-Ayerst, approved 01/01/1982). As of this review, OGD has approved the following ANDAs of Promethazine HCl Suppositories:

ANDA#	Firm	Strength	Date of Approval
84-901	Polymedica	25 mg	10/05/81
84-902	Polymedica	50 mg	10/05/81
87-165	G and W Lab	50 mg	08/14/87

13. **DOSAGE FORM** Suppositories (rectal administration)

14. **STRENGTH** 25 mg

15. **CHEMICAL NAME AND STRUCTURE**
Promethazine Hydrochloride. 10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)-.$C_{17}H_{20}N_2S$•HCl. 320.89. 58-33-3. Anti-emetic, antihistaminic.



16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**
Drug substance and drug product are listed in the USP 24. Method validation by FDA is not required. Type II DMF of the drug substance is adequate as of this review. All CMC issued have been resolved. Acceptable bioequivalence review was signed off on 11/30/01, and the bio acceptance letter was faxed to G&W on 12/14/01. Labeling approval summary has also been signed off.

Acceptable EER is dated 12/21/01

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable

19. **REVIEWER:**
Shing H. Liu, Ph.D.

DATE COMPLETED:
December 17, 2001
January 16, 2002 (after receiving telephone amendments)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-428

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-428 SPONSOR : G&W Laboratories

DRUG AND DOSAGE FORM : Promethazine Hydrochloride Suppositories, USP
STRENGTH(S) : 25 mg
TYPES OF STUDIES : In vivo bioequivalence study under fasting conditions.

CLINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : The bioequivalence study demonstrated that under fasting conditions, G&W Laboratories' Promethazine Hydrochloride Suppositories, USP, 25 mg, is bioequivale to Wyeth-Ayerst's Phenergan® Suppositories, 25 mg.

DISSOLUTION : The dissolution data for the 25 mg, are acceptable.

Note: In 1/07/02 correspondence, the firm accepted the Agency dissolution method and specifications (DBE review date: 11/30/01).

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic ___ New facility _ NO For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL /S/ _____ DATE : 1/30/02

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 1/30/02

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

INITIAL : /S/ _____ DATE : 1/30/02

A.2.1
Catterson

Promethazine Hydrochloride
Rectal Suppositories, USP, 25 mg
ANDA #40-428
Reviewer: Z.Z. Wahba
v:\firmsams\G&W\ltrs&rev\40428a2.001

G&W Laboratories
S. Plainfield, NJ
Submission date:
September 14, 2001

REVIEW OF AN AMENDMENT

BACKGROUND

The firm previously submitted an in vivo bioequivalence study (single dose) under fasting conditions comparing its 25 mg Promethazine Hydrochloride Suppositories USP, to the reference listed drug, Wyeth Ayerst's Phenergan® Rectal Suppository, 25 mg.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (DBE review date: 8/22/01) due to deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1

The firm was asked to develop a satisfactory in vitro dissolution method and establish in vitro dissolution specifications for its 25 mg promethazine hydrochloride suppositories. The Agency suggested the following dissolution method:

[ ]

Response to Comment #1

The firm provided the following dissolution data:

Table 1. In Vitro Dissolution Testing
I. Conditions for Dissolution Testing:
[ ]

II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #BB050400 Strength 25 mg			Reference Product Lot #9990697 Strength 25 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72.8	[redacted]	5.2	75.1	[redacted]	8.3
30	87.6	[redacted]	3.4	94.0	[redacted]	2.7
45	92.0	[redacted]	1.9	97.6	[redacted]	2.2
60	94.8	[redacted]	2.0	99.0	[redacted]	2.1

Table 2. In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

[redacted]

Test Drug: G&W's Promethazine Suppositories, 25 mg
Reference Drug: Wyeth-Ayerst Phenergan® Suppositories, 25 mg

II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #BB050400 Strength 25 mg			Reference Product Lot #A03869 Strength 25 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	41.7	[redacted]	64.2	10.1	[redacted]	37.6
30	52.9	[redacted]	52.8	14.1	[redacted]	51.5
45	63.9	[redacted]	37.6	20.8	[redacted]	104
60	72.2	[redacted]	27.1	25.1	[redacted]	110

Table 3. In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

[redacted]

Test Drug: G&W's Promethazine Suppositories, 25 mg
Reference Drug: Wyeth-Ayerst Phenergan® Suppositories, 25 mg

II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #BB050400 Strength 25 mg			Reference Product Lot #A03869 Strength 25 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	87.9	[redacted]	13.8	15.2	[redacted]	60.6
30	94.4	[redacted]	2.9	16.3	[redacted]	33.8
45	95.3	[redacted]	2.0	18.8	[redacted]	39.7
60	94.7	[redacted]	1.2	23.2	[redacted]	61.3

Table 4. In Vitro Dissolution Testing						
I. Conditions for Dissolution Testing:						
[redacted]						
Test Drug: G&W's Promethazine Suppositories, 25 mg Reference Drug: Wyeth-Ayerst Phenergan® Suppositories, 25 mg						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #BB050400 Strength 25 mg			Reference Product Lot #A03869 Strength 25 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	28.7	[redacted]	20.8	8.3	[redacted]	22.6
30	46.2	[redacted]	22.7	9.5	[redacted]	22.8
45	68.3	[redacted]	19.8	11.8	[redacted]	23.0
60	82.6	[redacted]	10.7	13.2	[redacted]	25.7

DBE Comment on the dissolution data (Not to be released under FOI):

1 [redacted]

2 [redacted]

4.

5

The response to comment #1 is acceptable.

Comment #2

The firm was asked to provide the assayed potency of the reference product.

Response to Comment #2

The RLD assay potency is

The response to comment #2 is acceptable.

Recommendations

1. The single-dose fasting bioequivalence study conducted by G&W Laboratories on its Promethazine Hydrochloride Suppositories, USP, 25 mg, Lot #BB050400, comparing it to Wyeth-Ayerst's Phenergan® 25 mg suppositories (lot #9990697) has been found acceptable by the Division of Bioequivalence. The study demonstrates that G&W Laboratories' Promethazine Hydrochloride Suppositories, USP, 25 mg, is bioequivalent to the RLD Wyeth-Ayerst's Phenergan® suppositories, 25 mg.

2. The dissolution testing conducted by the firm on its

Promethazine Hydrochloride Suppositories, USP, 25 mg, Lot #BB050400 is acceptable.

3. [redacted]

Not less than — (Q) of the labeled amount of Promethazine in the dosage form is dissolved in 30 minutes.

4. From bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

/S/ 11/27/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

11/27/01

/S/ /S/

Concur: _____ Date: 11/30/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-428 APPLICANT: G&W Laboratories, Inc.

DRUG PRODUCT: Promethazine Hydrochloride Suppositories USP, 25 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The following dissolution testing should be incorporated into your manufacturing controls and stability program:

[ ]

Not less than — (Q) of Promethazine Hydrochloride in the dosage form is dissolved in 30 minutes.

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

Sincerely yours,

"1ST"

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-428 SPONSOR : G&W Laboratories

DRUG AND DOSAGE FORM : Promethazine Hydrochloride Suppositories, USP
STRENGTH(S) : 25 mg
TYPES OF STUDIES : In vivo bioequivalence study under fasting conditions.

CLINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : The bioequivalence study demonstrated that under fasting conditions, G&W Laboratories' Promethazine Hydrochloride Suppositories, USP, 25 mg, is bioequivalent to Wyeth-Ayerst's Phenergan® Suppositories, 25 mg.

DISSOLUTION : The dissolution data for the 25 mg, are acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic ___ New facility _ NO For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 11/27/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 11/27/01

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

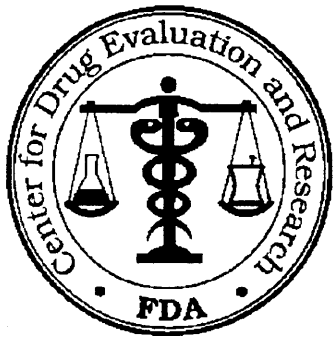
INITIAL : /S/ ___ DATE : 11/30/01

BIOEQUIVALENCY AMENDMENT

ANDA 40-428

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP - 4 2001



TO: APPLICANT: G&W Laboratories, Inc. TEL: 908-753-2000

ATTN: Hindy Schiff FAX: 908-753-9264

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 19, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Promethazine Hydrochloride Suppositories USP, 25 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

1.1 N

SEP - 4 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-428 APPLICANT: G&W Laboratories, Inc.

DRUG PRODUCT: Promethazine Hydrochloride Suppositories USP, 25 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The in vitro dissolution testing conducted on your promethazine hydrochloride suppositories, 25 mg, Lot # BB050400 is incomplete. Please develop a satisfactory in vitro dissolution method and establish in vitro dissolution specifications for 25 mg promethazine hydrochloride suppositories. The Agency recommends the following dissolution method:

[ ]

2. Please provide information on the assayed potency of the reference product.

3. In future ANDA applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section.

Sincerely yours,

/S/

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

Promethazine Hydrochloride
Rectal Suppositories, USP, 25 mg
ANDA #**40-428**
Reviewer: Z.Z. Wahba
v:\firmsams\G&W\ltrs&rev\40428s.D00

G&W Laboratories
S. Plainfield, NJ
Submission date:
December 19, 2000

Review of A Single Dose Bioequivalence Study, And Dissolution Data

OBJECTIVE:
To review:

- G&W Laboratories single dose *in vivo* bioequivalence study under fasting conditions comparing its 25 mg Promethazine Hydrochloride Suppositories USP, to the reference listed drug, Wyeth Ayerst's Phenergan® Rectal Suppository, 25 mg.

- Comparative dissolution data for both the test and reference drug products.

BACKGROUND:

Promethazine hydrochloride is a phenothiazide derivative. It is an H_1 receptor blockng agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemitic effects.

RLD: Wyeth-Ayerst's Phenergan® Rectal Suppository, 25 mg

BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

Study Information:

Protocol #001984
Sponsor: G&W Laboratories
Clinical Facility: [redacted]

Analytical Facility: [redacted]

Principle Investigator: [redacted]
Study Director: [redacted]

Treatment Plan:

Test or Reference:	Test	Reference
Product Name:	Promethazine HCl	Phenergan®
Manufacturer:	G&W	Wyeth-Ayerst
Manufacture Date:	05/11/00	N/A
Expiration Date:	N/A	5/01
ANDA Batch Size:	[redacted] units	N/A

Batch/Lot Number:	BB050400	9990697
Assay Potency:	99.1%	Not given
Content Uniformity:	98.2%	Not given
Strength:	25 mg	25 mg
Dosage Form:	suppository	suppository
Dose Administered:	1 X 25 mg	1 X 25 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	12 hours	12 hours

Study Plan:

Study design	Single dose, randomized, two-way crossover study under fasting conditions.
No. of subjects	• 56 subjects enrolled (Protocol specifies 48 subjects and 8 alternates). • 48 subjects completed (subjects #1-30, 32, 34-44, and 46-51, for details, see drop-outs). • 43 subjects used for statistical analysis (for details, see subjects with bowel movements section, below).
Drop-outs	• Subjects #31 & 45 were withdrawn from the study by the Medical Advisor after the 1-hour blood draw in Period-2 and 4-hour blood draw in Period-1, respectively, due to having bowel movements and adverse events. Subjects #31 & 45 were replaced with subjects #49 and 51, respectively. • Subject #33 elected to withdraw from the study for personal reasons after the 8-hour blood draw in Period-1. Subject #33 was replaced with subject #50.
Clinical Dates	Period I: 9/21/00; Period II: 10/05/00
Analytical study dates (start-end dates)	10/10/00 to 11/01/00
Wash out period	14 days
Blood sampling	Pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 60 hours post-dosing.

Subjects with bowel movements during the study

The following subjects had bowel movements within 12 hours after drug administration:

Subject #	Period	Formulation	Hours (Post-dose)
10	1	B	6.4 hours

11	1	A	7.0 hours
17	1	A	8.2 hours
31*	2	B	22 minutes (subject stated that he saw the suppository in his stool)
43	1	A	10.7 hours
45*	1	B B	50 minutes and 58 minutes
48	1	B	11.4 hours

* Subject was withdrawn from the study.

Demographic Data	• Gender: 56 males • Race: 53 Caucasians (94.6%), 2 Blacks (3.6%), 1 Oriental (1.8%) • Age: Average 32.4 year (20-45 years) Zero subjects < 18 years 47 subjects between 18-40 years 9 subjects between 41-64 years zero subjects between 65-75 years zero subjects between > 75 years • Height (cm): Average 175.6 (162-189 cm) • Weight (lb): 73.01 kg (58.6-87.1 kg)

Adverse Events:

Ten subjects experienced a total of forty-five (45) adverse events during this study. All medical events were mild to moderate. Of the forty-five adverse events, fifteen were unrelated related to the study drug, sixteen were remotely related to the study drug, and fourteen were possibly study drug related (pages #312 and 317-323, vol. C1.1).

Assay Methodology: **(NOT TO BE RELEASED UNDER FOI)**

Analytical method	[redacted]
Analyte	[redacted]
Pre-Study Validation	[redacted]
Sensitivity (LOQ)	[redacted]
Quality control (QC) samples	[redacted]
QC samples validation	[redacted]
Linearity	[redacted]
Calibration curve validation	[redacted]
Recovery	[redacted]

Stability	[redacted]
During Study Validation	
Sensitivity (LOQ)	
Quality control (QC) samples	
QC samples validation	
Linearty	
Calibration curve validation	

Repeat assays during the BE study: Less than 3% of the total number of samples were repeated. There were no repeats for pharmacokinetic reasons.

Statistical Analyses:

The plasma concentrations and pharmacokinetic parameters of promethazine under fasting conditions were analyzed using the SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for promethazine are summarized in the tables below:

Table #1
Mean Plasma Concentrations (ng/mL)
of Promethazine Under Fasting Conditions
(n=43)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.16	0.36	0.03	0.13	5.03
2	0.73	0.76	0.27	0.37	2.67
3	1.42	1.20	0.78	0.81	1.82
4	1.96	1.45	1.28	1.37	1.53
5	2.99	2.16	1.91	1.38	1.57
6	3.55	2.40	2.55	1.86	1.39
7	4.81	3.42	3.72	2.49	1.29
8	5.13	3.50	4.23	2.91	1.21
9	5.62	3.97	4.64	2.89	1.21
10	5.65	3.98	4.95	3.33	1.14
12	5.66	4.22	5.22	3.93	1.08
16	4.08	3.49	3.99	3.42	1.02
24	2.53	2.26	2.46	2.08	1.03

36	1.34	1.49	1.30	1.24	1.02
48	0.84	1.11	0.77	0.96	1.08
60	0.52	0.83	0.49	0.73	1.06

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #2

Summary of Pharmacokinetics Parameters (Promethazine) Under Fasting Conditions (n=43)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	150.48	139.46	135.64	119.60	1.11
AUCT	130.06	110.45	117.77	97.97	1.10
CMAX	6.20	4.33	5.60	3.89	1.11
KE	0.05	0.01	0.05	0.01	0.97
*LAUCI	111.67	0.76	103.54	0.72	1.08
*LAUCT	98.33	0.76	90.24	0.73	1.09
*LCMAX	4.97	0.69	4.60	0.64	1.08
THALF	16.96	7.60	15.98	4.91	1.06
TMAX	10.03	1.98	10.44	1.91	0.96

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table #3

LSMeans and 90% Confidence Intervals (Promethazine) (n=43)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	111.84	103.69	1.08	96.90	120.07
LAUCT	98.46	90.36	1.09	96.53	123.00
LCMAX	4.97	4.60	1.08	95.57	122.11

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML

Comment on the fasting study (Promethazine):

The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).

Note: Subjects #10, 11, 17, 43, and 48 were not included in the statistical analysis. These subjects were removed from statistical analysis since they had bowel movements that occurred before two times the median Tmax observed in the study. This is consistent with the principles in the CDER Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*, Oct. 2000.

Promethazine pharmacokinetics show high intrasubject variability. The root mean square error values for lnAUCt, lnAUCi, and lnCmax were 0.33, 0.30, and 0.34, respectively. Since the posting of the above guidance, the Division of Bioequivalence has been asking firms developing promethazine HCl suppository products to use a replicate design with average bioequivalence statistical analysis. G&W Laboratories initiated their study prior to the posting of the guidance in October 2000.

Formulation (Not to be released under FOI)

Ingredient	Amount per mg
Hard Fat, NF	
White Wax,	
Glyceryl Monostearate, NF	
Colloidal Silicon Dioxide, NF	
Promethazine HCl, USP ( )	
Ascorbyl Palmitate, NF	
Total	1400.00

The COMIS database indicates that Hard Fat has been approved at the level of in NDA #11-127 (Able Labs' Prochlorperazine Suppository, Comis product #003).

All other inactive ingredients are within approved limits of the FDA Inactive Ingredient Guide, January, 1996.

DISSOLUTION:

The firm provided the following dissolution data:

In Vitro Dissolution Testing						
I. Conditions for Dissolution Testing:						
[redacted]						
Test Drug: G&W's Promethazine Suppositories, 25 mg Reference Drug: Wyeth-Ayerst Phenergan® Suppositories, 25 mg						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #BB050400 Strength 25 mg			Reference Product Lot #9990697 Strength 25 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72.8	[redacted]	5.2	75.1	[redacted]	8.3
30	87.6	[redacted]	3.4	94.0	[redacted]	2.7
45	92.0	[redacted]	1.9	97.6	[redacted]	2.2
60	94.8	[redacted]	2.0	99.0	[redacted]	2.1

Comment on the dissolution data:

1. The USP 24 does not recommend dissolution testing under the promethazine suppository monograph.

2. On 11/01/99, G&W Laboratories asked (ODG 99-407) the OGD to provide comments on the dissolution requirements for its drug promethazine suppository, 25 mg. The office recommended (OGD 99-407, dated: 12/9/99) the following method:

[redacted]

3. Recently, the DBE reviewed an application on [redacted] review date 6/28/01).

[redacted]

In writing to Alpharma, the Division recommended the following dissolution method:

[redacted]

DEFICIENCIES

1. The firm's dissolution data are unacceptable. The firm is requested to conduct the dissolution method following the current FDA method:

[redacted]

2. The assay potency of the reference product was not reported in submission.

RECOMMENDATIONS

1. The single-dose fasting bioequivalence study conducted by G&W laboratories on its promethazine hydrochloride suppositories, 25 mg, lot #BB050400, comparing it to Wyeth-Ayerst's Phenergan® 25 mg suppositories (lot #9990697) is incomplete.

2. The in vitro dissolution testing conducted by G&W laboratories on its promethazine hydrochloride suppositories, 25 mg, Lot #BB050400, is not acceptable. The dissolution testing should be conducted using the FDA recommended method given below:

[ ]

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

8/3/01

RD INITIALED BDAVIT /S/
FT INITIALED BDAVIT /S/ Date: 8/3/01

Concur: /S/ Date: 8/22/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

fw

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-428 APPLICANT: G&W Laboratories, Inc.

DRUG PRODUCT: Promethazine Hydrochloride Suppositories USP, 25 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The in vitro dissolution testing conducted on your promethazine hydrochloride suppositories, 25 mg, Lot # BB050400 is incomplete. Please develop a satisfactory in vitro dissolution method and establish in vitro dissolution specifications for 25 mg promethazine hydrochloride suppositories. The Agency recommends the following dissolution method:

[ ]

2. Please provide information on the assayed potency of the reference product.

3. In future ANDA applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section.

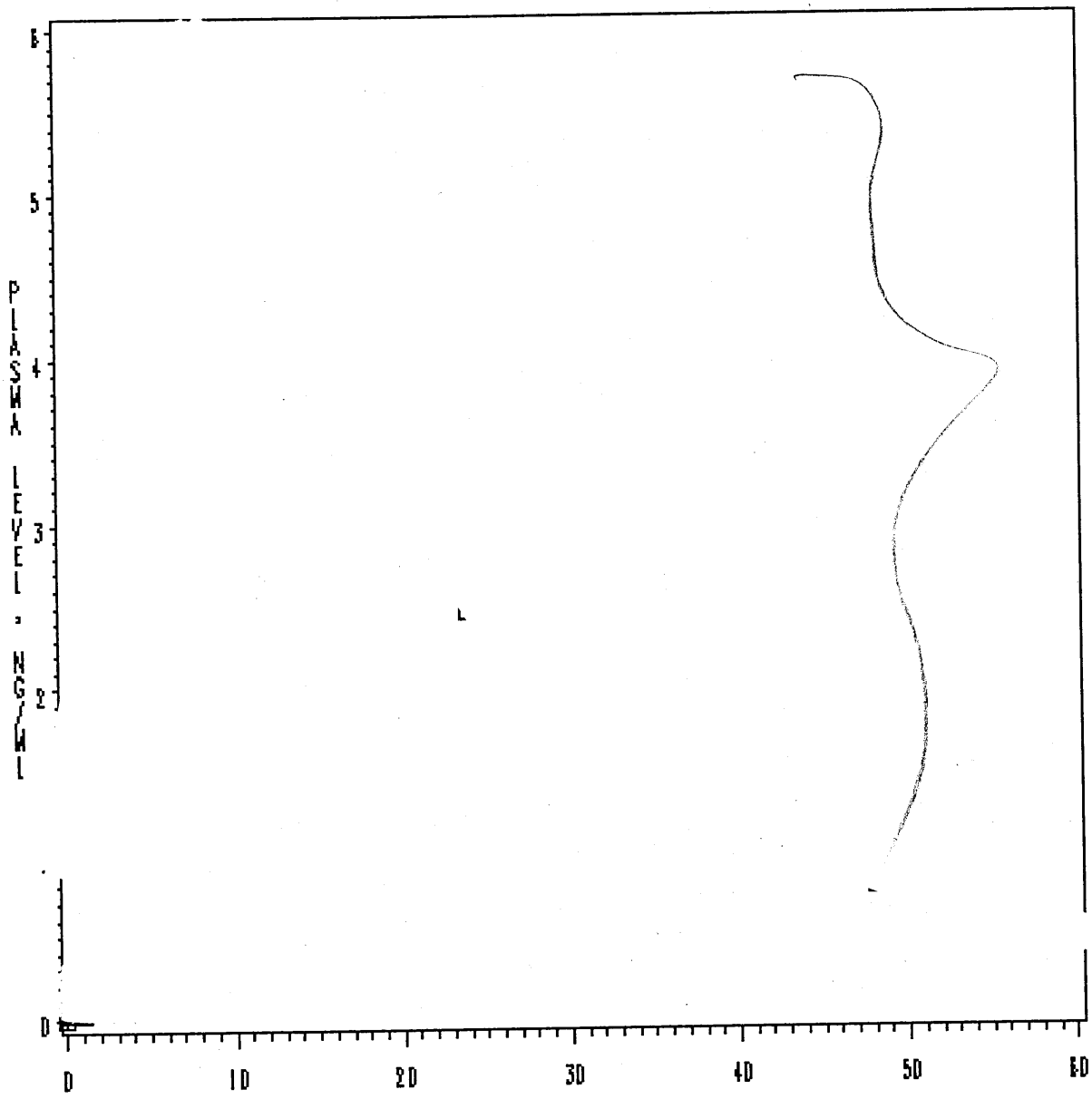
Sincerely yours,

/S/

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

FIG P—1 . PLASMA PROMETHAZINE LEVELS

PROMETHAZINE HCL SUPPOSITORIES, 25 MG, ANDA #40428
UNDER FASTING CONDITIONS
DOSE=1 X 25 MG



1=TEST(GBV LABORATORIES) 2=REF(WYETH-AYERST)

28

CC: ANDA #40-4~~2~~1
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba ~~ZZW~~ 8/3/01
HFD-658/ B. Davit BWD 8/3/01
HFD-650/ D. Conner ~~for~~ 8/22/2001

v:\firmsam\G&W\ltrs&rev\404~~2~~1s.d00
28

BIOEQUIVALENCY - Incomplete submission date: 12/19/00

1. FASTING STUDY (STF) Strength: ~~0.5 mg~~ 25 mg
Clinical: [redacted] Outcome: ~~AC~~ IC

Analytical: [redacted]

OUTCOME DECISIONS: ~~INCOMPLETE~~ incomplete
~~Acceptable~~

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-428

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	40-428
Date of Submission:	December 19, 2000
Applicant's Name:	G & W Laboratories, Inc.
Established Name:	Promethazine Hydrochloride Suppositories USP, 25 mg
Proprietary Name:	Promethegan™

Labeling Deficiencies:

1. **NOTE:** Submit draft copies of foil labels for our review and comments.

2. **CARTON** – 12 individually wrapped suppositories
   Satisfactory in **draft** as of the December 19, 2000 submission.

3. **PACKAGE INSERT**
   CLINICAL PHARMACOLOGY
   Last paragraph, first two sentences –

   Delete these sentences from the text.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the OPDRA? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? The firm already utilizes this name in the market place for the same drug but a different strength. Therefore, I did NOT submit this to OPDRA.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels		X	

and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product; Phenergan Suppositories; NDA 10-926 approved January 22, 1988.

1a. Note that this ANDA has a sister application that was APPROVED August 14, 1987; ANDA 87-165; for the 50 mg promethazine HCL suppositories. Since the proprietary name

OPDRA for review.

1b. Note that G & W Labs intends to utilize separate package inserts for their suppositories.

2. Patent/ Exclusivities:
Patent Data – NDA 10-926

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	**None**	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 10-926

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
NDA: Refrigerate suppositories. Dispense in a well-closed container.
ANDA: Store refrigerated between 2° to 8°C (36° to 46°F). Dispense in a well-closed container.
USP: Preserve in tight, light-resistant containers, and store in a cold place.

We will not ask the firm to revise.

4. Product Line:
The innovator markets their 25mg suppository as individually wrapped in cartons of 12.

The applicant proposes the same as RLD

5. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 1929, Vol B. 1.1.

6. All manufacturing will be done by G & W Laboratories. (See pg. 1992 in vol. B. 1.1)

Date of Review: 7/27/01 Date of Submission: 12/19/00
Primary Reviewer: Jim Barlow Date: 8/2/01

Team Leader: John Grace /S/ , Date: 8/6/2001

cc:
ANDA 40-428
DUP/DIVISION FILE
HFD-613/JBarlowforDCaterson/JGrace (no cc)
V:\FIRMSAM\G&W\LTRS&REV\40428na1.l
Review

APPROVAL SUMMARY

ANDA: 40-428

DRUG PRODUCT: Promethazine Hydrochloride Suppositories USP, 25 mg

FIRM: G & W Laboratories, Inc.

DOSAGE FORM: Suppositories (rectal administration)

STRENGTH: 25 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER acceptable on 1/30/02

BIO STUDY: Acceptable Bioequivalence review was signed off on 11/30/01.

VALIDATION: Method validation is not required.

STABILITY:
In the 01/08/02 telephone amendment, G&W updated the specifications for stability in response to Bioequivalence Division's comments (see bio letter dated 12/14/01 and G&W's subsequent bio amendment dated 01/07/02) and CMC telephone amednment request dated 12/06/01). The current specifications for dissolution have been revised.

Since G&W revised the dissolution specifications, they have provided stability data in the 01/08/02 chemistry amendment. G&W presented drug release data at 30 min for three process validation lots and the bio batch (#BB050400) stored at 2-8°C (label storage conditions) at the time the samples were tested. The test results met the revised dissolution specifications.

G&W also presented comparable dissolution data for the bio batch batch (#BB050400) at 6 months and 19 months storage at 2-8°C (label storage conditions). The 6 months data was obtained previously during the stability study for this lot of product. (NOTE: G&W informed FDA in the 12/17/01 telephone conversation that when they conducted accelerated stability studies on the bio batch, they did not check the 30 minute time point!).

G&W showed that there is no statistical difference between the dissolution performance of the bio batch stored at either 6 or 19 months. Based on this data, G&W stated that the dissolution performance at 24 months for this lot is expected to be comparable to the observed results at 6 and 19 months.

G&W's current specifications for stability (effective 01/07/02) are as follows (see telephone amendment for chemistry dated 01/08/02):

Test Item	Specification	
Description	A wax, white, firm suppository, with absence of fissures	
Average weight	1.33-1.54 gm/suppository	
Onset of melt	NMT [redacted]	
Dissolution	NMT [redacted] in 30 min. [redacted]	
Assay (active)	[redacted] Label Claim	
Ascorbyl Palmitate	[redacted]	
Related substances	Individual impurities: NMT [redacted]	
	Total impurities: NMT [redacted]	
	[redacted]	NMT [redacted]
	[redacted]	NMT [redacted]
	[redacted]	NMT [redacted]
	[redacted]	NMT [redacted]
	Unknown	NMT [redacted]
	Total	NMT [redacted]

LABELING: Labeling was approved as of 12/28/01.

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch: [redacted]

SIZE OF STABILITY BATCHES: same as the bio batch

PROPOSED PRODUCTION BATCHES: [redacted]

STATUS OF DMF for the DRUG SUBSTANCES: Adequate as of 05/17/00

/S/

Review Chemist:_____ **DATE:** 01/23/2002
Shing H. Liu, Ph.D.

/S/

Team Leader:_____ **DATE:** 1/28/02
James M. Fan

V:\Firmsam\g&W\ltrs&rev\40428app.sum.doc

TELEPHONE MEMO

ANDA/DMF#: ANDA 40-428

FIRM: G&W Laboratories, Inc.
Telephone No.: 908-753-2000 Ext 3064

PARTICIPANTS:
FDA: Paul Schwartz, Deputy Director, Chem I
Jim Fan, Team Leader
Shing Liu, Senior Reviewer
Bonnie McNeal, Project Manager

/S/ 12/7/01 /S/ 12/5/01 /S/ 12/10/01 /S/ 12/7/01

G&W: Dr. Rosch Vora, VP Scientific Affairs
Dr. Bala Nayar, Dir. of Product Development
Dr. Michael Catrara, Dir. Analytical Research and Development
Ronald Greenblatt, President of G&W
Hindy Schiff, Regulatory Affairs
Joan Alban, Regulatory Affairs

DATE: December 6, 2001 10:00AM

SUBJECT: Promethazine HCl Suppositories USP, 25 mg

REQUESTED BY: FDA

Dr. Schwartz stated that in a fax dated November 29, 2001 the firm had listed specifications for viscosity of NMT ——— and an extrapolated specification for ascorbyl palmitate of NLT ——— He asked the firm how they arrived at these specs.

Dr. Cutrara answered that they extrapolate from 3 months of room temperature data (this is the accelerated condition, since the product is to be stored at refrigerated conditions), to get the —— value. The data from 0-3 months of stability studies gives values of ——, and the firm doesn't see degradation or impurities.

Dr. Schwartz explained that if the firm wants a spec of —— they need data to support it. They must show that —— of ascorbyl palmitate, which works as ———. To provide data for the spec they would need to test the product to see if the ——— at 24 months. It is important to be aware that one can never extrapolate past 3

months of accelerated data to set a specification. The spec must be based on data.

Also, Dr. Schwartz noted that the firm changed their viscosity spec from NMT [redacted] to NMT [redacted] He asked for an explanation and also asked if the product was a semi-solid or a solid.

The firm answered that they consider their product a solid. During the manufacturing process the [redacted]

Dr. Schwartz asked what data the firm had to support their [redacted]

Dr. Schwartz explained that the firm set a spec without explanation and then changed it without explanation. This is the reason for the telephone call. Also, the Agency has a hard time accepting a tentative spec or one for information only. Also, he wondered why there was a viscosity spec at all if it was not meaningful.

[redacted]

The firm was asked to submit the additional information as a telephone amendment if they could submit it within ten days.

Filename: \\CDS008\WP51F99\FIRMSAM\G&W\TELECONS\40428.12-06-01.doc

CC: ANDA 40-428
Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-428

CORRESPONDENCE

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
Sales Office: (800) 922-1038 • Fax: (908) 753-5174

January 8, 2002

NDA

ORIG AMENDMENT

Ms. Sarah Ho, Project Manager
OGD/CDER/FDA
HFD-600 Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

Our Reference
ANDA 40-428
Promethazine Hydrochloride Suppositories USP, 25 mg

Dear Ms. Ho:

Reference is made to the telephone call of December 17, 2001 from Dr. Jim Fann/Team Leader and Dr. Shing Liu/ Reviewing Chemist of the FDA Chemistry Division regarding the dissolution specifications of *Not less than — (Q) in 30 minutes* provided by the Division of Bioequivalence on December 14, 2001. During this conversation we were requested to a) provide data to support the specification and b) to update our Quality Control specifications.

In support of these requests we are attaching the following documentation:

- Dissolution of Promethazine Suppositories USP, 25 mg, Product Code 0526 Using [redacted] *(Attachment 1)*
- Updated Quality Control Finished Product and Stability Specifications for Promethazine Hydrochloride Suppositories USP, 25 mg *(Attachment 2)*

On December 21, 2001 G&W sent a fax amendment to the Division of Bioequivalence requesting a dissolution specification of Not less than — Q) in 45 minutes *(Attachment 3)*. On January 7, 2002 we received a fax from the Division of Bioequivalence responding to our amendment with the following comments:

G&W Laboratories, Inc.

Promethazine Hydrochloride Suppositories USP, 25 mg
ANDA #40-428

- Your request to change the dissolution specification from "Not less than — (Q) in 30 minutes" to "Not less than — (Q) in 45 minutes" is denied.

[ ]

test product should meet the following specifications:

> Not less than — (Q) of the labeled amount of Promethazine Hydrochloride in the dosage form is dissolved in 30 minutes.

Please be advised that on January 7, 2001 we acknowledged these comments and have revised our specification to comply with the above described dissolution requirement of: Not less than —, (Q) of the labeled amount of Promethazine Hydrochloride in the dosage form is dissolved in 30 minutes *(Attachment 4)*.

If you have any questions, please contact me at the above telephone number and/or fax number.

Thank you.

Sincerely,
G&W Laboratories, Inc.

Hindy Schiff

Hindy Schiff
Vice President, Quality Assurance/ Regulatory Affairs

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
Sales Office: (800) 922-1038 • Fax: (908) 753-5174

BIOAVAILABILITY

ORIG AMENDMENT
IN/AB

September 14, 2001

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
OGD/CDER/FDA
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCY AMENDMENT

Our Reference
ANDA 40-428
Promethazine Hydrochloride Suppositories USP, 25 mg

Dear Dr. Conner:

Reference is made to your correspondence dated and faxed September 4, 2001 regarding our original abbreviated new drug application for Promethazine Hydrochloride Suppositories USP, 25 mg submitted on December 19, 2000 pursuant to § 505(j) of the Federal Food, Drug and Cosmetic Act.

In accordance with 21 CFR §314.96, we have responded to each of the deficiencies in the following pages of this submission.

If you have any questions, please contact me at the above telephone number and/or fax number.

Thank you.

CENTER FOR DRUG
SEP 17 2001
OGD
EVALUATION AND RESEARCH

Sincerely,
G&W Laboratories, Inc.

Hindy Schiff

Hindy Schiff
Vice President, Quality Assurance/ Regulatory Affairs

0526 deficiency

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
Sales Office: (800) 922-1038 • Fax: (908) 753-5174

August 22, 2001

N/AF

ORIG AMENDMENT

Mr. William Peter Rickman, Acting Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Our Reference
ANDA #40-428
Promethazine Hydrochloride Suppositories USP, 25 mg

Labeling Deficiencies

Dear Mr. Rickman:

Reference is made to the labeling review dated and faxed August 6, 2001 relative to our ANDA 40-428 submission for Promethazine Hydrochloride Suppositories USP, 25 mg.

We have responded to each of the labeling deficiencies in the following pages of this submission.

Thank you.

Sincerely,
G&W Laboratories, Inc.

Hindy Schiff

Hindy Schiff
Vice President, Quality Assurance/ Regulatory Affairs

0526 label def

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

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ORIG AMENDMENT
N/AM.

July 13, 2001

Mr. Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville Maryland 20855

Minor Amendment

Our Reference
ANDA 40-428

Dear Mr. Buehler:

Reference is made to your correspondence dated June 5, 2001, relative to our abbreviated new drug application submitted pursuant to §505(j) of the Federal Food, Drug and Cosmetic Act for Promethazine Hydrochloride Suppositories USP, 25 mg.

We have responded to each of the minor deficiencies pertaining to the CMC section of the abbreviated new drug application in the following pages of this submission.

Thank you.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 23 2001
DGD

Sincerely,
G&W Laboratories, Inc.

Hindy Schiff
Vice-President, Quality Assurance/ Regulatory Affairs Department

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G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
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NEW CORRESP
BIOAVAILABILITY

June 18, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 19 2001
OGD

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N

Attention: Mr. Steve Mazzella

Telephone Amendment To Bioequivalence Division

Original Abbreviated New Drug Application
Promethazine Hydrochloride Suppositories USP, 25 mg
ANDA #40-428

RE: *Project No. 001984*
Comparative, Randomized, Singe-Dose, 2-Way Crossover Bioavailability Study of G&W and Wyeth-Ayerst (Phenergan®) 25 mg Promethazine HCl Suppositories in Healthy Adult Males

Dear Mr. Mazzella:

As discussed during our telephone conference call of June 14, 2001 enclosed please find a copy of the FDA.1 file for the above study. This file contains the plasma concentration and pharmacokinetic data (with a header line explaining each data category) along with hard copies of these data. Although plasma and pharmacokinetic data from all analyzed subjects are included in this file, the primary analysis in the report excludes subjects Nos. 10, 11, 17, 43 and 48 in keeping with the provisions of the protocol concerning defecation. Further details on the issue can be found in the final report.

Additionally, please be advised that the Quality Control laboratory of G&W Laboratories, Inc. located at 111 Coolidge Street, South Plainfield, NJ 07080 performed dissolution testing for Promethazine Hydrochloride Suppositories USP, 25 mg.

Thank you.

Sincerely,
G&W Laboratories, Inc.

Hindy Schiff
Vice President, Quality Assurance/ Regulatory Affairs

0526TelephoneAmendment

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
Sales Office: (800) 922-1038 • Fax: (908) 753-5174

January 22, 2001

Mr. Martin Shimer
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

Amendment

Original Abbreviated New Drug Application
Promethazine Hydrochloride Suppositories USP, 25 mg
ANDA #40-428

Dear Mr. Shimer:

Reference is made to our original abbreviated new drug application for Promethazine Hydrochloride Suppositories USP, 25 mg, filed on December 20, 2000 in accordance with 21 CFR §314.94.

As per our discussion on January 12, 2001 please amend this original application to include the following:

1) Revised Form FDA 356h to include USP nomenclature under the section designated Product Description
2) Signed original Generic Drug Enforcement Act (GDEA) Debarment Certification
3) Accelerated stability report revised to include initial stability data points
4) Side by side box packaging comparison (G&W vs. Innovator)
5) Revised [redacted] DMF letter (foil manufacturer) authorizing FDA to access their file on behalf of G&W Laboratories, Inc.

Thank you.

Sincerely,
G&W Laboratories, Inc.

John Mhin/FOR
Hindy Schiff, Vice President
Quality Assurance/ Regulatory Affairs

0526Amend

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 26 2001
OGD

G&W LABORATORIES, INC.

111 Coolidge Street, South Plainfield, New Jersey 07080-3895

General Office: (908) 753-2000 • Fax: (908) 753-9264
Sales Office: (800) 922-1038 • Fax: (908) 753-5174

December 19, 2000

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01-FEB-2001
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[S]

FEDERAL EXPRESS

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
Promethazine Hydrochloride Suppositories USP, 25 mg

Dear Mr. Buehler:

Pursuant to §505(j) of the Federal Food, Drug and Cosmetic Act, we submit herewith an abbreviated new drug application for the drug product Promethazine Hydrochloride Suppositories USP, 25 mg.

The archival and review copies for this abbreviated new drug application are assembled in accordance with 21 CFR §314.94. These copies are presented in a total of 10 volumes: 5 for the archival copy and 5 for the review copy (1 Volume/ Chemistry Section, 4 Volumes/Pharmacokinetic Section).

The application contains a full report of the *in vivo* bioavailability study. This study compares Promethazine Hydrochloride Suppositories USP, 25 mg, manufactured by G & W Laboratories, Inc. to the reference listed drug, Phenergan® Suppositories, 25 mg, manufactured by Wyeth Laboratories, Inc.

This also certifies that concurrent with the filing of this ANDA, a true copy of the technical section of the ANDA was sent to our local FDA District Office.

Please direct any comments regarding this ANDA to Hindy Schiff at the above address or telephone number.

CENTER FOR DRUG
RECD
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OGD
EVALUATION AND RESEARCH

Thank you.

Sincerely,

Hindy Schiff, Vice President
Quality Assurance/ Regulatory Affairs

ANDA 40-428

G & W Laboratories, Inc.
Attention: Hindy Schiff
111 Coolidge Street
South Plainfield, NJ 07080

FEB

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated January 12, 2001 and your correspondence dated January 22, 2001.

NAME OF DRUG: Promethazine Hydrochloride Suppositories USP, 25 mg

DATE OF APPLICATION: December 19, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 20, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

/S/ for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research