CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 087165 Supplements

Trade Name : PROMETHGAN 50MG SUPPOSITORIES

Generic Name: Promethazine Hydrochloride

Sponsor : G & W Laboratories

Approval Date: Numerous Dates

ANDA 87-165/S-001

JUL 23 1991

G & W Laboratories, Inc.
Attention: Carol Frankel
111 Coolidge Street
South Plainfield, New Jersey 07080

Dear Madam:

Reference is made to your supplemental new drug application dated February 20, 1991, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for PROMETHEGAN (Promethazine Hydrochloride Suppositories USP, 50 mg.

Reference is also made to your communication dated July 5, 1991, amending this supplement.

The supplemental application provides for revised carton labeling (12s) to include a new proprietary name (PROMETHEGAN).

We have completed the review of this supplemental application and it is approved. Our letter of August 14, 1987, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely yours,

Kent C. Johnson for 7-23-91

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc;
HFD-638
HFD-600
HFC-130/JAllen
JPhillips/TPoux
hab 7/22/91
87165L.S
approval

Jerry Phillips 7/23/91

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 201-753-2000 FAX 201-753-9264

July 5, 1991

Roger L. Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Reference: ANDA 87-165/S-001
Promethazine HCl Suppositories, 50 mg

Dear Dr. Williams:

Reference is made to your letter dated May 28, 1991 responsive to our supplement dated April 25, 1991.

As per our commitment, submitted herewith are twelve (12) copies of printed cartons for the 12 package size which we believe satisfies the points you have raised.

Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, New York 10022
(212) 755-2339

Promethazine Hydrochloride Suppositories USP 50 mg

Caution: Federal law prohibits dispensing without prescription. For Rectal Administration.

12 Suppositories

NDC 0713-0132-12

JUL 23 1991

Promethazine Hydrochloride Suppositories USP

50 mg

BOXALL, INC.

Each suppository contains 50 mg promethazine hydrochloride with ascorbyl palmitate and polysorbate 80 in a specially blended base of saturated vegetable fatty acids.

Directions: Remove foil wrapper and insert one suppository well up into rectum as directed by a physician.

Usual Dosage: See insert for detailed information regarding dosage and precautions for use.

Note: Store in a cold place 2°–8°C (36°–46°F).

Warning: Keep this and all drugs out of reach of children. In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

G&W Laboratories, Inc.
South Plainfield, NJ 07080

NDC 0713-0132-12

10-1321GW3

MAR 2 8 1991

ANDA 87-165/S-001

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

Dear Madam:

Reference is made to your supplemental new drug application dated February 20, 1991, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Promethazine Hydrochloride Suppositories, 50 mg.

The supplemental application provides for revised carton labeling (12's) to include a new proprietary name (PROMETHEGAN).

The supplemental application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. The dosage form should be part of the established name. In addition, include USP as follows:

   Promethazine Hydrochloride
   Suppositories USP
   50 mg.

2. In the spirit of 21 CFR 201.56(b) labeling shall not be promotional in tone. In this regard, delete the following:

   "Established since 1919, G & W Laboratories is one of the largest manufacturers of quality suppositories in the United States. We take special care to ensure that all products are of the finest quality you can buy".

3. "FOR RECTAL ADMINISTRATION" should be made more prominent.

4. You have not submitted carton labeling for your 25 package size. Please comment.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or

withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

for 3-27-91

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-600 Jerry Phillips 3/27/91
JPhillips/TPoux
np/3-25-1991
87165L.S
Unapproval
3/27/91

Carton labeling
needs revised
3-22-91
Phillips

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 201-753-2000 FAX 201-753-9264

February 20, 1991

Dr. Roger Williams, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
7500 Standish Place
Rockville, Md. 20855

NDA NO. [redacted] SLDW
NDA SUPP. [redacted]
FPL

Reference: ANDA 87-165
Promethazine HCl Suppositories
50 mg.

Dear Dr. Williams:

Reference is made to your letter dated December 3, 1990 responsive to our periodic report dated September 14, 1990 and a telephone conversation between Mr. Jerry Philips of the Agency and Ms. Carol Frankel representing G & W Laboratories, Inc. on February 7, 1991. The following are our responses to the points raised in your letter:

I-Submitted herewith are twelve (12) printed copies of the revised carton.

II-All of the corrections with respect to the package insert will be made at the time of the next printing and when available twelve (12) copies will be submitted as a supplement to this application.

With reference to your comment about USP XXII specifications, we wish to assure you that the drug substance is tested in accordance with it. The drug product is tested according to the ANDA approved which conforms to USP XXII standards.

Thank you for including this information in the file of reference.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57th Street
New York, N.Y. 10022
(212) 755-2339

D Mills mar 91

MAY 15 1991

ANDA 87-165/S-002

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

Dear Madam:

Reference is made to your supplemental new drug application dated April 25, 1991, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for PROMETHEGAN (Promethazine Hydrochloride - Suppositories USP) 50 mg.

The supplemental application provides for revised carton labeling (25s).

We have completed the review of this supplemental application and it is approved. Our letter of August 14, 1987, detailed the conditions relating to the approval of this abbreviated application.

We acknowledge your commitment to submit revised carton labeling for your package size of 12. This should be submitted as an amendment to S-001.

The material submitted is being retained in our files.

Sincerely yours,

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-83
HFD-600/JPhillips/TPoux
HFC-130/JAllen
np/5-13-91
87165L.S
APPROVAL

Created second letter for ANDA 87-165/S-002 because the first letter was sent to the firm with no signature.

Willie Turner
05/28/91

ANDA 87-165/S-002

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

Dear Madam:

Reference is made to your supplemental new drug application dated April 25, 1991, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for PROMETHEGAN (Promethazine Hydrochloride Suppositories USP) 50 mg.

The supplemental application provides for revised carton labeling (25s).

We have completed the review of this supplemental application and it is approved. Our letter of August 14, 1987, detailed the conditions relating to the approval of this abbreviated application.

We acknowledge your commitment to submit revised carton labeling for your package size of 12. This should be submitted as an amendment to S-001.

The material submitted is being retained in our files.

Sincerely yours,

Lewis C. Helmer for

5-24-91

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-83
HFD-600/JPhillips/TPoux
HFC-130/JAllen
np/5-13-91
87165L.S
APPROVAL

6/19

FPL for cartons in Satisfactory
5-13-91
Jerry Phillips RPh

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 201-753-2000 FAX 201-753-9264

April 25, 1991

NDA NO. [illegible] SUPPL NO. SL-002
NDA SUPPL FOR Labeling Rev

FPL

Roger L. Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Reference: ANDA 87-165/S-001
Promethazine HCl Suppositories, 50 mg

Dear Dr. Williams:

Reference is made to your letter dated March 28, 1991 responsive to our February 20, 1991 supplemental new drug application. We have incorporated your suggestions and new carton labelling (12's) is being printed and when they are available we will submit them.

We are enclosing twelve (12) copies of printed cartons for the 25 package size which we believe satisfies the points you have raised.

Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, New York 10022
(212) 755-2339

APPROVED

MAY 15 1991

Directions: Remove foil wrapper and insert one suppository well up into rectum as directed by a physician.

Usual Dosage: See insert for detailed information regarding dosage and precautions for use.

Note: Store in a cold place 2° - 8°C (36° - 46°F).

Warning: Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

PROMETHEGAN™

PROMETHAZINE HYDROCHLORIDE
Suppositories 50 mg

10-13225GW1

PROMETHEGAN™
PROMETHAZINE HYDROCHLORIDE
Suppositories 50 mg

NDC 0713-0132-25

PROMETHEGAN™

PROMETHAZINE HYDROCHLORIDE
Suppositories 50 mg

Each suppository contains: 50 mg promethazine hydrochloride with ascorbyl palmitate and polysorbate 80 in a specially blended base of saturated vegetable fatty acids.

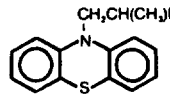
Caution: Federal law prohibits dispensing without prescription.

For Rectal Administration
25 Suppositories

G•W Laboratories, Inc.
South Plainfield, N.J. 07080

PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES, USP

DESCRIPTION: Promethazine Hydrochloride a phenothiazine derivative is designed chemically as a 10-[2-(Dimethylamino) propyl] phenothiazine monohydrochloride with the following structural formula:



·HCl

$C_{17}H_{20}N_2S \cdot HCl$

MW 320.88

NOV 8 1991

Each rectal suppository contains 50 mg promethazine hydrocholride USP with ascorbyl palmitate and polysorbate 80 in a specially blended base of saturated vegetable fatty acids.

CLINICAL PHAMACOLOGY: 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 lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.

Promethazine is an H, receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, 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-demethylpromethazine are the predominant metabolites appearing in the urine.

INDICATIONS AND USAGE: Promethazine is useful for: Perennial and seasonal allergic rhinitis.

Vasomotor rhinitis.

Allergic conjunctivitis due to inhalant allergens and foods

Mild, uncomplicated allergic skin manifestations or 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 post-operative 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 prescence of promethazine hydrocholride. 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 may cause marked drowsiness or may 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 therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedative, 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 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: Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning the 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 mg and 12.5 mg/kg of promethazine. These doses are from approximately 6 to 16.7 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 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, 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 (one 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 doses 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 · The treatment of overdosage with promethazine 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. Attention should be given to the re-establishment 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 of the depressant effects of promethazine are not reversed by naloxone. Avoid analeptics, which may cause convulsions.

Severe hypotention usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient 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 oral 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 eight to twelve 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 tablets, syrup, or rectal suppositories, 12.5 mg 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 and adults is 25 mg. 12.5 mg to 25 mg doses may be repeated as necessary at four to six hour intervals. For nausea and vomiting in children, 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 post-operative period, the average dose is 25 mg, repeated at four to six hour intervals as necessary.

SEDATION: Promethazine hydrochloride 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 the oral route or 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 hydrochloride in 12.5 mg 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 in adults.

Promethazine hydrochloride suppositories are not recommended for children under 2 years of age.

HOW SUPPLIED: Available in the following strength and package sizes:
Promethazine Hydrochloride Suppositories USP 50 mg, white bullet shaped suppositories sealed in silver foil, 12 in a box - NDC 0713-0132-12 and boxes of 25 - NDC 0713-0132-25.

Caution: Federal law prohibits dispensing without prescription.

STORAGE: Store in a cold place 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

8-1320GW11
Rev. 1/91

ANDA 87-165/S-003

G & W Laboratories, Inc.
Attention: Carol Frankel
111 Coolidge Street
South Plainfield, New Jersey 07080

NOV 8 1991

Dear Madam:

Reference is made to your supplemental new drug application dated October 25, 1991, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Promethazine Hydrochloride Suppositories USP 50 mg.

The supplemental application provides for revised package insert labeling to include changes in the WARNINGS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections.

We have completed the review of this supplemental application and it is approved. Our letter of August 14, 1987, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely yours,

Ken Johnson for

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11-8-91

cc;
HFD-638
HFD-600
HFC-130/JAllen- Jerry Phillips 11/7/91
JPhillips/TPoux
hab 11/5/91
87165L.S
approval
HFD-82

11/7/91

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 908-753-2000 FAX 908-753-9264

PPL for insert is satisfactory 11-4-91 JMH

October 25, 1991

Dr. Roger Williams, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NDA NO. _____ ANDA NO. SL 003
NAME OF DRUG FOR _____

Reference: ANDA 87-165
Promethazine HCl Suppositories
50 mg.

Dear Dr. Williams:

Reference is made to our supplement dated February 20, 1991 to the above referenced ANDA. As stated in point II of that submission enclosed herewith are twelve (12) copies of the printed insert which includes the corrections requested in your letter of December 3, 1990.

Thank you for including this information in file of reference.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57th Street
New York, NY 10022
(212) 755-2339

ANDA 87-165/S-004

G & W Laboratories, Inc.
Attn: Carol Frankel (Consultant)
333 East 57th Street
New York, N.Y. 10022

DEC - 1 1993

Dear Madam:

This is in reference to your supplemental new drug application dated August 5, 1993, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Promethazine Hydrochloride Suppositories USP, 50 mg.

Reference is also made to your request for an expedited review on September 29, 1993 and to your correspondence dated October 11, 1993.

The supplemental application provides for an alternate supplier of Promethazine Hydrochloride USP new drug substance.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81. Please note that your accelerated stability conditions should be at 25-30°C.

The material submitted is being retained in our files.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	FEER ID
☒ Original ☐ Follow-Up ☐ FUR	11/2/93	(301)594-0310	[redacted]

REQUESTOR'S NAME	DIVISION	MAIL CODE
Elise Murphy	OGD/Chem. I.	HFD-633

APPLICATION AND SUPPLEMENT NUMBER
ANDA # 87-165/S-004

BRAND NAME	ESTABLISHED NAME
Promethegan™	Promethazine Hydrochloride ~~Suppos~~ Supossitories, USP

DOSAGE AND STRENGTH	STERILE
50 mg Suppositories	☐ YES ☒ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
SUP	

APPLICANT'S NAME
G & W Laboratories, Inc.

ADDRESS
111 Coolidge Street
South Plainfield, N.J. 07080-3895

AGENT: Ms. Carol Frankel
333 E. 57th Street
New York, New York 10022

COMMENTS

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
3.				
4.				
5.				

FOR HFD-324 USE ONLY:		
	CSO Charles Kopes	DATE RECEIVED 11/8/93
	CGMP COMPLIANCE STATUS Acceptable	DATE 11/12/93

Chemistry Manufacturing and Controls Review of Promethazine Hcl Suppositories

ANDA 87-165/S-004

NAME AND ADDRESS OF AGENT
G & W Laboratories
Attn: Carol Frankel
333 East 57th Street
New York, New York 10022

NAME OF APPLICANT:
G & W Laboratories, Inc.
111 Coolidge Street
South Plainfield,
New Jersey 07080-3895

PURPOSE OF AMENDMENT/SUPPLEMENT
An expedited review request was made due to an abrupt discontinuation of their New Drug Substance supplier for Promethazine HCl.

DATE(S) OF SUBMISSION(S)
Original Supplement: August 5, 1993
Expedited Review: September 29, 1993

PHARMACOLOGICAL CATEGORY	TRADE NAME
Antihistamine	Promethegan

NONPROPRIETARY NAME
Promethazine HCL

DOSAGE FORM	POTENCY	RX OR OTC
Suppositories	50 mg	R_x

REMARKS AND CONCLUSION
Approval

Reviewer	Date Completed
Elise Murphy	November 22, 1993

cc: ANDA 87-165
Division File
FIELD COPY

Endorsements:

HFD-633/E. Murphy/11-22-93 Elise Murphy 11/29/93
HFD-633/D. Gill/ABC/11-22-93 DS Gill 11.29.93
X:\WPFILE\BRANCH1\MURPHY\87165S04.REM
F/T by dvw/11-29-93.

3.1

ORIGINAL

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

October 11, 1993

NDA SUPPLEMENT
SCov 4 AC

Dr. Jim Wilson, Branch I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 87-165 Supplement 4
Promethazine HCl Suppositories,50mg.

Dear Dr. Wilson:

Reference is made to our request for expedited review of of the above cited supplement and recent telephone conversations concerning proof of the active raw material supply problem. Therefore attached hereto is a letter from G & W Labs, Inc. to me explaining the supply problems they have had and their referenced letter from the U.S. supplier.

Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
(212) 755-2339

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 908-753-2000 FAX 908-753-9264

changed to expedited review requested on October 13, 1993 Barr Memo 11/2/93

SC-0004/AX

September 29, 1993

Mr. Douglas Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 87-165 Supplement 4
Promethazine HCl Suppositories, 50mg.

EXPEDITED REVIEW REQUESTED

Dear Mr. Sporn:

This is an amendment to our submission to the above cited application dated August 5, 1993 assigned as Supplement 4 by the agency. That submission explained that the current supplier of the active ingredient no longer supplies this drug and therefore we have made a supplementary submission to provide for a new supplier.

We have no active ingredient except that from the new supplier and we need to manufacture a batch of product in order to avoid supply interruption. We therefore are requesting expedited review of this submission.

Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
(212) 755-2339

ORIGINAL

G&W LABORATORIES, INC.
111 Coolidge Street, South Plainfield, New Jersey 07080-3895 908-753-2000 FAX 908-753-9264

August 5, 1993

Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NDA NO. _____ REF. NO. Seq 4
NDA SUPPL FOR Supplier #2

Reference: ANDA 87-165
Promethazine HCl Suppositories, 50mg.

Dear Dr. Williams:

Enclosed herewith is a supplement to provide for an additional supplier of active bulk promethazine HCl:

We have included a letter from the supplier authorizing reference to their for this drug. Certificates of analysis from both the supplier and G&W Laboratories, Inc. are included herewith.

A batch of suppositories has been made with this material and the supporting documents are also included as well as 3 months of accelerated stability data.

The supplier currently approved in our application no longer supplies this drug and we are therefore in a position of not being able to continue to manufacture this product until this new supplier is approved.

Thank you for your kind cooperation and prompt attention to this matter.

Respectfully yours,

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N.Y. 10022
(212) 755-2339

3.1

ANDA 87-165/S-005, S-006

G & W Laboratories, Inc.
Attention: Carol Frankel
333 East 57 St.
New York, NY 10022

Dear Madam:

This is in reference to your supplemental new drug applications dated April 2, 1996, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Promethazine HCl Suppositories USP, 50 mg.

Reference is also made to your amendment dated February 7, 1996.

The supplemental applications provide for:

S-005: A new supplier of aluminum foil

S-006: New filling/molding equipment from

We have completed the review of these supplemental applications, and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Yours sincerely,

3/14/97

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

G&W LABORATORIES, INC.

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

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

March 20, 1997

WITHDRAWN WD 5C005 WD 5C006

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA: 87-165 S-005, S-006
Promethazine HCl Suppositories, USP, 50mg.

Dear Mr. Sporn:

Reference is made to your letter of approval dated March 14, 1997 which was just received. Please note that a letter dated March 7, 1997 was sent by G & W Laboratories, Inc. withdrawing these supplements because it determined some of these new manufacturing methods need to be optimized and therefore changed. Under the circumstances we suggest that this approval letter be withdrawn since the company will not be manufacturing the product under the process submitted.

We apologize for the inconvenience to the agency and we thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

FEDERAL

MAR 21 1997

GENERIC DRUGS

G&W LABORATORIES, INC.

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

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

March 7, 1997

NEW CORRESP
NC TO 50005
50006

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA : 87-165 S-005, S-006
Promethazine HCl Suppositories USP, 50 mg.

Dear Mr. Sporn:

Reference is made to ANDA 87-165 S-005, S-006 for Promethazine HCl Suppositories USP, 50 mg. dated April 2, 1996 providing for new suppliers of aluminum foil and new filling/molding equipment from G & W Laboratories, Inc. recently reviewed this new manufacturing method and determined some procedures need to be optimized and therefore changed. The new procedures when completed development will be submitted for approval along with the revised supplements S-005 and S-006.

G & W Laboratories, Inc. at this time wishes to withdraw these supplements without prejudice. Thank you for your kind cooperation with respect to this matter.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, NY 10022
phone (212) 755-2339
fax (212) 754-0704

RECEIVED
MAR 1 1 1997
GENERIC DRUGS

ANDA 87-165/S-005, S-006 Review # 2

NAME AND ADDRESS OF APPLICANT

Firm:
G & W Laboratories, Inc.
111 Coolidge St.
South Plainfield, NJ 07080-3895

Agent:
Carol Frankel
333 East 57 St.
New York, NY 10022

PURPOSE OF AMENDMENT/SUPPLEMENT

S-005: A new supplier of aluminum foil

S-006: New filling/molding equipment from

DATE(S) OF SUBMISSION(S)

April 2, 1996	Original submission
October 16, 1996	*NA letter*
February 7, 1997	**Amendment ***THIS REVIEW*****

PHARMACOLOGICAL CATEGORY	TRADE NAME
Antihistaminic	N/A

NONPROPRIETARY NAME
Promethazine HCl Suppositories, USP

DOSAGE FORM	POTENCY	RX OR OTC
Suppositories	50 mg	Rx

RELATED IND/NDA/DMF N/A

STERILIZATION N/A

LABELING N/A

BIOEQUIVALENCY STATUS N/A

ESTABLISHMENT INSPECTION N/A

REMARKS AND CONCLUSION
Recommend: APPROVAL.

Reviewer: J. L. Smith Date Completed: February 14, 1997

cc: ANDA 87-165
Division File
Field Copy
HFD-600/Reading File

Endorsements:
HFD-623/J.Smith/ JLSmith 2/14/97
HFD-623/V.Sayeed/ Vilayet Sayeed 2/14/97
Y:\NEW\FIRMSAM\G&W\LTRS&REV\87165AP2.S06
F/T by:

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080 908-753-2000 FAX 908-753-9264

February 7, 1997

NDA SUPPL AMENDMENT

SC-005/AM

SC-006/AM

MINOR AMENDMENT

Rashmikant M. Patel, Ph.D., Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 87-165/S-005, S-006
Promethazine HCl Suppositories USP, 50 mg.

Dear Dr. Patel:

Reference is made to your letter dated October 18, 1996 concerning supplements to ANDA 87-165 providing for additional filling/molding equipment and additional suppliers of foil. The following are our responses to the chemistry deficiencies raised:

"1. Please provide a short, concise description of the packaging materials that will be obtained from the new suppliers (e.g., size, shape, material(s) of construction, dimensions, etc.)."

G&W Laboratories has decided that this supplement will cover only the therefore the foil description is:

"2. The films are described as being What effect does this variation have on the size and shape of the finished drug product?"

The various sizes refer to which has no effect on the composition of the foil or the size and shape of the finished product. As noted above G&W Laboratories has decided to limit this supplement to the

"3. The Incoming Inspection Report for the makes no provision for checking the quality of the printing."

Please note this supplement only covers the which is supplied unprinted. Printing is done on line at G&W Laboratories, Inc.

RECEIVED
FEB 11 1997
GENERIC DRUGS

"4. Please explain the reference to and on the Incoming Inspection Report for the and why there is no corresponding reference for the

The core is the central device around which the foil is wound. Attached is a revised specification sheet which includes the core details.

"5. Can ink from the printed side of the film leave a residue on the side that contacts the drug product? Please describe any restrictions on or specification for the printing ink.

It is unlikely that the ink would leave a residue on the product which touches the not the outside foil which is printed. Attached is a MSDS for the ink which gives some information about this ink.

"6. was reviewed and was found to be inadequate. The DMF holder is being informed of the inadequacies. These supplemental applications will not be approved until all the inadequacies have been satisfactorily addressed.

At this time we wish to withdraw reference to as a supplier. Therefore this supplement will only include foil supplied by

We trust these supplements are now complete. Should you have any questions or need clarifications, please feel free to contact me.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, New York 10022
Phone: (212) 755-2339
Fax: (212) 754-0704

ANDA 87-165/S-005, S-006

G & W Laboratories, Inc.
Attention: Carol Frankel
333 East 57 St.
New York, NY 10022

OCT 18 1996

Dear Madam:

This is in reference to your supplemental new drug applications dated April 2, 1996, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Promethazine HCl Suppositories USP, 50 mg.

The supplemental applications provide for:

S-005: Two new suppliers of aluminum foil.

S-006: New filling/molding equipment from

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Please provide a short, concise description of the packaging materials that will be obtained from the new suppliers (e.g., size, shape, material(s) of construction, dimensions, etc.).

2. The films are described as being What affect does this variation have on the size and shape of the finished drug product?

3. The Incoming Inspection Report for the makes no provision for checking the quality of the printing.

4. Please explain the reference to ' and on the Incoming Inspection Report for the and why there is no corresponding reference for the

5. Can ink from the printed side of the film leave a residue on the side that contacts the drug product? Please describe any restrictions on or specification for the printing ink.

6. was reviewed and was found to be inadequate. The DMF holder is being informed of the inadequacies. These supplemental applications will not be approved until all the inadequacies have been satisfactorily addressed.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Yours sincerely,

10/17/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 87-165
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-623/J.Smith/9-25-96 JL Smith 9/27/96
HFD-623/V.Sayeed, Ph.D./9-25-96 V. Sayeed 9/27/96
HFD-617/J.Wilson/CSO/9-26-96 9/30/96
X:\NEW\FIRMSAM\G&W\LTRS&REV\87165NA1.S06
F/T by: bc/9-26-96

NOT APPROVABLE: MINOR

ANDA 87-165/S-005, S-006 Review # 1

NAME AND ADDRESS OF APPLICANT

Firm: Agent:

G & W Laboratories, Inc.
111 Coolidge St.
South Plainfield, NJ 07080-3895

Carol Frankel
333 East 57 St.
New York, NY 10022

PURPOSE OF AMENDMENT/SUPPLEMENT

S-005: Two new suppliers of aluminum foil

S-006: New filling/molding equipment from

DATE(S) OF SUBMISSION(S)

April 2, 1996

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Antihistaminic	N/A	Promethazine HCl Suppositories, USP

DOSAGE FORM	POTENCY	RX OR OTC
Suppositories	50 mg	Rx

REMARKS AND CONCLUSION

Recommend: NOT APPROVABLE. Minor amendment.

Reviewer: J. L. Smith Date Completed: September 25, 1996

cc: ANDA 87-165
Division File
Field Copy
HFD-600/Reading File

Endorsements:
HFD-623/J.Smith/ JL Smith 9/25/96
HFD-623/V.Sayeed/ Vilaya K Sayeed 9/25/96.
X:\NEW\FIRMSAM\G&W\LTRS&REV\87165NA1.S06
F/T by:

0j

NDA NO. _____ REF. NO. Scn5

NDA SUPPL FOR Supplement Sent

G&W LABORATORIES, INC. 111 Coolidge Street, South Plainfield, New Jersey 07080-3895 • 908-753-2000 • Gen. Fax 908-753-9264 • Sales Fax 908-753-5174

RECEIVED April 1996

APR 04 1996

Dr. Charles Ganley, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NDA NO. _____ REF. NO. Scn6 GENERIC DRUGS

NDA SUPPL FOR Info Sent

RE: ANDA 87-165
PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES, 50 mg

Dear Dr. Ganley:

We are submitting herewith in duplicate a supplement to include the addition of new state of the art filling/molding equipment and two additional aluminum foil suppliers. In support of these improvements, we are including a side by side comparison of the existing methods to the proposed new ones as well as support manufacturing, component and stability data.

The current equipment was supplied by and the new ones are from Since G & W Laboratories, Inc. has two machines, a batch was filled and molded in each of the machines, designated as I and II, to demonstrate the equivalence to the current process on file. Since we also want to qualify two additional suppliers of aluminum foil, we used one of these for product processed in each machine. These were then placed on stability study.

The enclosed data includes a copy of the current master formula record for the and executed batch record for the lot processed on the For ease of review we have included a side by side comparison of the process. Stability data for each batch as well as the specifications and DMF reference letters for the two additional aluminum foil suppliers are included.

This data demonstrates the equivalence to the current process and packaging components on file in this application. If you have any questions or need any additional information, please feel free to contact me.

Respectfully yours,

Carol Frankel

Carol Frankel
Consultant in Regulatory Affairs
333 East 57 Street
New York, N. Y., 10022
phone (212) 755-2339
fax (212) 754-0704

G&W LABORATORIES, INC. 75 Years OF EXCELLENCE
Quality Value Innovation