CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84902

CORRESPONDENCE

AUG 16 1982

NDA 84-902

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Alcon Laboratories, Inc.
Attention: Roger O. Metzler
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

Gentlemen:

This letter concerns reporting requirements under section 505(j) of the Federal Food, Drug, and Cosmetic Act for drug products that have been approved in accordance with the provisions of section 505(b) of the Act.

The new drug regulations section 310.300(b)(4) sets forth requirements for periodic reports which are to be submitted for each product covered by an approved abbreviated new drug application (ANDA), whether or not the drug is marketed. Our records indicate that no reports has been received for Promethacon (Promethazine Hydrochloride) Suppositories, 50 mg.

Failure to submit required reports is a ground for withdrawal of approval of the new drug application under section 505(e) of the Act. A copy of the required transmittal form FD-2252 (Transmittal of Periodic Reports for Drugs for Human Use) is enclosed for your convenience.

If you have ceased to market this drug product and you anticipate no further marketing of it in the future, you may, if you wish, request that the Food and Drug Administration withdraw approval of the abbreviated new drug application. If you elect to request withdrawal of approval, you must also indicate that you voluntarily waive your opportunity for a hearing. We would then proceed to publish in the Federal Register a notice withdrawing approval of the application, stating that marketing of the drug has been discontinued and the applicant has requested withdrawal of approval of the application and waived opportunity for a hearing. The grounds for withdrawal of the approval will be that the applicant has requested withdrawal of approval because the product is no longer marketed.

If you choose neither to submit the required reports nor to make such a request with waiver within 30 days of receipt of this letter, we will proceed to publish a notice of opportunity for hearing on a proposal to withdraw approval of the abbreviated new drug application on the grounds of failure to report.

Please submit all communications regarding this ANDA with the following specific address information:

National Center for Drugs and Biologics
Division of Generic Drug Monographs (HFD-530)
ROOM #16-70
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

/S/ 8/16/82

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

Enclosure: FD Form 2252

cc:
DAL-DO
HFD-530
HFD-320
DRosen

REPLY REQUESTED

NDA 84-902

AF 27-736

Alcon Laboratories, Inc.
Attention: Mr. Richard A. Hamer
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

SEP 11 1975

Gentlemen:

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

NAME OF DRUG: Promethacon Suprettes (promethazine hydrochloride suppositories) 50 mg.

DATE OF APPLICATION: September 9, 1975

DATE OF RECEIPT: September 9, 1975

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 NDA number shown above.

Sincerely yours,

/S/

9/10/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO

HFD-530
HFD-616
HFD-310
JLMeyer/wlb/9-10-75
Ack.

/S/ 9/10/75

b. Ambodryl Elixir (NDA 8-476); and

c. Ambodryl Syrup (NDA 8-745); Parke, Davis & Co., Joseph Campau at the River, Detroit, Mich. 48232.

2. *Preparations containing chlorpheniramine maleate.* a. Chlor-Trimeton Tablets and Syrup (NDA 6-921); and

b. Chlor-Trimeton Repetabs Tablets (NDA 7-638); Schering Corp., 60 Orange Street, Bloomfield, N.J. 07003.

3. *Preparations containing cyproheptadine hydrochloride.* a. Periactin HCl Tablets (NDA 12-649); and

b. Periactin HCl Syrup (NDA 13-220); Merck Sharp & Dohme, Division Merck & Co., Inc., West Point, Pa. 19486.

4. *Preparations containing diphenhydramine hydrochloride.* a. Benadryl Syrup, Kapseals (capsules), Elixir, Emplets (enteric coated tablets), and Powder (for pharmaceutical dispensing purposes) (NDA 5-845); Parke, Davis & Co.

5. *Preparations containing diphenylpyraline hydrochloride.* a. Diafen Tablets (NDA 9-970); Riker Laboratories, 19901 Nordhoff Street, Northridge, Calif. 91326.

6. *Preparations containing promethazine hydrochloride.* a. Phenergan Tablets (NDA 7-935); and

b. Phenergan Syrup (NDA 8-381); and

c. Phenergan Rectal Suppositories (NDA 10-926 and NDA 11-689); Wyeth Laboratories Division, American Home Products Corp., Post Office Box 8299, Philadelphia, Pa. 19101.

7. *Preparation containing pheniramine maleate.* a. Trimeton Tablets (NDA 6-461); Schering Corp.

8. *Preparations containing pyrilamine maleate.* a. Neo-Antergan Maleate Tablets (NDA 6-290 and 7-119); Merck Sharp & Dohme.

9. *Preparations containing tripelennamine hydrochloride or tripelennamine citrate.* a. Pyribenzamine Tablets (NDA 5-914); Ciba Pharmaceuticals Co., Division of Ciba Corp., 556 Morris Avenue, Summit, N.J. 07901; and

b. Pyribenzamine Lontabs (sustained release tablet) (NDA 10-533); Ciba Pharmaceutical Co., Division of Ciba Corp.

c. Pyribenzamine Elixir (NDA 5-914); Ciba Pharmaceutical Co., Division of Ciba Corp.

The drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drugs without approval.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that:

1. Bromodiphenhydramine Hydrochloride in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, allergic reactions to insect bites; physical

OTC Product
NOT in this DESI
See DESI 6412

[DESI 6290; Docket No. FDC-D-324; NDA 5-845, etc.]

CERTAIN ANTIHISTAMINIC PREPARATIONS FOR ORAL OR RECTAL ADMINISTRATION

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following antihistaminic preparations for oral or rectal administration:

1. *Preparations containing bromodiphenhydramine hydrochloride.* a. Ambodryl Kapseals (NDA 7-984); and

6/18/71

allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; motion sickness; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for migraine headache including allergic migraine: "histamine headache;" tissue preservative action; prevention or reduction of severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients; and "other conditions of a similar nature" (considered too broad to allow meaningful evaluation).

2. Chlorpheniramine Maleate in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis, neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus, pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients.

3. Cyproheptadine Hydrochloride in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; prutitus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; pruritus of chicken pox; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for: migraine headache including allergic migraine; "histamine headache;" tissue preservation action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients.

4. Diphenhydramine Hydrochloride in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus; intractable insomnia and insomnia predominant in certain medical disorders.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis, contact dermatitis (including dermatitis venenata or poison ivy) chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use of desensitization procedures and when essential to use therapy known to be sensitizing; quieting the hyperactive emotionally disturbed child; prevention of postoperative nausea and vomiting; maintenance of normal sinus rhythm following recent conversion from atrial fibrillation; nausea and vomiting of early pregnancy; spasmolysis in gastrointestinal and other allergies characterized by smooth muscle spasm.

c. Lacking substantial evidence of effectiveness for migraine headache including allergic migraine, "histamine headache," tissue preservation action, prevention or reduction of severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage), potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics, prevention of allergic reactions to injection of allergenic substances, antiemetic effect in postoperative patients, antitussive action; Meniere's disease, nocturnal leg cramps, leg cramps of pregnancy, functional dysmenorrhea.

5. Diphenylpyraline Hydrochloride in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for: migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the actual of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients; nausea and vomiting of pregnancy.

6. Promethazine hydrochloride in conventional oral or rectal dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus; intractable insomnia and insomnia predominant in certain medical disorders; prevention and control of the more severe, hazardous nausea and vomiting of pregnancy.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritis; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and

(other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for: migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; nausea and vomiting of reflex origin; shortening of labor; prevention of allergic reactions to injection of allergenic substances; and "allergic conditions amenable to antihistamine therapy" (considered too broad to allow meaningful evaluation).

7. Pheniramine maleate in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus; prevention or relief of motion sickness.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for: migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of the central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients; and "pheniramine maleate is of value clinically in the prevention and relief of many allergic manifestations" (considered too broad to allow meaningful evaluation).

8. Pyrilamine maleate in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitis; neurodermatitis circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or posion ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for: migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients.

9. Tripelennamine Hydrochloride or Citrate in conventional oral dosage form is:

a. Effective or probably effective for the indications described in the "Indications" section which follows. The probably effective indications are: Mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus.

b. Possibly effective for bronchial asthma; spasmodic bronchial cough; atopic dermatitis; neurodermatitus circumscripta; eczematoid dermatitis; allergic eczema; allergic dermatitis; contact dermatitis (including dermatitis venenata or poison ivy); chemotoxic dermatitis; generalized pruritus; pruritus ani and vulvae; secretory otitis media; prophylaxis of allergic reactions to contrast media; pruritus of jaundice; prophylaxis of penicillin and (other) drug reactions; pruritus of allergic dermatoses including contact dermatitis; relief of insect stings; use in desensitization procedures and when essential to use therapy known to be sensitizing.

c. Lacking substantial evidence of effectiveness for migraine headache including allergic migraine; "histamine headache;" tissue preservative action; prevention or reduction in severity of sequellae of oral surgery (pain, trismus, edema, and hemorrhage); potentiation of the action of central nervous system depressants with resultant reduction of dosage of narcotic analgesics; prevention of allergic reactions to injection of allergenic substances; antiemetic effect in postoperative patients. The indication "many other "allergic conditions" is considered too broad to allow meaningful evaluation.

10. Chlorpheniramine Maleate and Tripelennamine Hydrochloride in sustained action dosage forms for oral administration are:

a. Probably effective for indications evaluated as effective and probably effective for conventional oral dosage forms of these drugs. (See paragraphs 2 and 9 above.)

b. Possibly effective and lacking substantial evidence of effectiveness for the same indications listed in these categories for the conventional oral dosage forms of these drugs in paragraphs 2 and 9 above.

B. *Conditions for approval and marketing of drugs having an effective classification.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* a. These preparations are in a conventional dosage form suitable for oral administration.

b. Diphenhydramine hydrochloride may also be in a powder form suitable for prescription compounding.

c. Promethazine hydrochloride may also be in a suppository form suitable for rectal administration.

2. *Labeling conditions.* *a.* The labels bear the statement, "Caution: Federal law prohibits dispensing without prescription."

b. Each drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows:

INDICATIONS

i. *Bromodiphenhydramine Hydrochloride.*

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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.

Dermographism.

As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Mild, local allergic reactions to insect bites.

Physical allergy.

Minor drug serum reactions characterized by pruritus.

ii. *Chlorpheniramine Maleate.*

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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.

Dermographism.

As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Mild, local allergic reactions to insect bites.

Physical allergy.

Minor drug and serum reactions characterized by pruritus.

iii. *Cyproheptadine Hydrochloride.*

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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
iv. *Diphenhydramine Hydrochloride.*
Perennial and seasonal allergic rhinitis.
Vasomotor rhinitis.
Allergic conjunctivitis due to inhalant allergens and foods.
Mild, uncomplicated allergic skin manifestations of urticaria and angiodema.
Amelioration and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Parkinsonism (including drug-induced) in the elderly unable to tolerate more potent agents.
Mild cases of parkinsonium (including drug-induced) in other age groups.
In other cases of parkinsonism (including drug-induced) in combination with centrally acting anticholinergic agents.
Active and prophylactic treatment of motion sickness.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
Intractable insomnia and insomnia predominant in certain medical disorders.
v. *Diphenylpyraline Hydrochloride.*
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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
vi. *Promethazine Hydrochloride.*
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 and prevention of allergic reactions to blood plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive 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 effect in postoperative patients.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
Intractable insomnia and insomnia predominant in certain medical disorders.
Prevention and control of severe, hazardous nausea and vomiting of pregnancy.
vii. *Pheniramine Maleate.*
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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As thereapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
Prevention and relief of motion sickness.
viii. *Pyrilamine maleate.*
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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Mild allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.
ix. *Triplennamine Hydrochloride and citrate.*
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 and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
Dermographism.
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
Mild, local allergic reactions to insect bites.
Physical allergy.
Minor drug and serum reactions characterized by pruritus.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling, an abbreviated supplement for updating information, and adequate data to show the biologic availability of the drug in the formulation which is marketed as described in paragraphs (a)(1)(i), (ii), and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application, to include adequate data to assure the biologic availability of the drug in the formulation which is or is intended to be marketed, as described in paragraph (a)(3)(ii) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

d. For indications for which the drug has been classified as probably effective (included in the "Indications" section above) and possibly effective (not included in the "Indications" section), continued use as described in (c), (d), (e), and (f) of that notice.

C. *Conditions for marketing drugs having no indication classified as effective.* 1. Within 60 days of the date of publication of this announcement in the FEDERAL REGISTER, the holder of any previously approved new drug application for a drug which is classified in paragraph A above as lacking substantial evidence of effectiveness is requested to submit a supplement to his application, as needed, to provide for revised labeling which deletes those indications for which substantial evidence of effectiveness is lacking and which contains an "Indications" section in accord with that described below. Such supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest possible time, and the revised labeling should be put into use within the 60-day period. Failure to delete such indications and to put the revised labeling into use within 60 days after the date of publication hereof in the FEDERAL REGISTER may result in a proposal to withdraw approval of the new drug application.

2. If any such preparation is on the market without an approved new drug application, its labeling should be revised to delete all claims for which substantial evidence of effectiveness is lacking as described in paragraph A above and to be in accord with this notice. Failure to delete such indications and to put the revised labeling into use within 60 days after the date of publication hereof in the FEDERAL REGISTER may cause the drug to be subject to regulatory proceedings.

3. Indications for which the drug is regarded as probably effective or possibly effective may continue to be used for 12 months or 6 months, respectively, following the date of this publication, to allow additional time within which holders of

previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness, including evidence that the drug has the sustained action or prolonged effect claimed.

4. To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well organized, and include data from adequate and well controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

5. At the end of the 6-month and 12-month periods, any such data will be evaluated to determine whether there is substantial evidence of effectiveness of the drug for such uses. The conclusions concerning the drug will be published in the FEDERAL REGISTER. If no studies have been undertaken or if the studies do not provide substantial evidence of effectiveness, procedures will be initiated to withdraw approval of the new drug application for the drug, pursuant to the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act. Withdrawal of approval of the application will cause any such drug on the market to be a new drug for which an approval is not in effect.

6. Labeling revised pursuant to this notice should take into account the comments of the Academy, furnish adequate information for safe and effective use of the drug, be in accord with the guidelines for uniform labeling (§ 3.74) published in the FEDERAL REGISTER of February 6, 1970, and recommend use of the drug (for the probably effective indications) as follows: (The possibly effective indications may also be included for 6 months).

INDICATIONS

(The "Indications" sections are the same as those listed for the conventional dosage forms of chlorpheniramine maleate and tripelennamine hydrochloride in paragraph B.2 above.)

D. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any related drug for human use offered for the indications for which substantial evidence of effectiveness is lacking to be a new drug for which an approved new drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER.

3. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing, together with a well organized and full factual analysis of the clinical and other investigation data that the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

4. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

A copy of the Academy's report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 6290, directed to the attention of the following appropriate office, and addressed (unless otherwise specified), to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Original abbreviated new drug application (identify as such): Drug Efficacy Study Implementation Project Office (BD-5), Bureau of Drugs.

Request for hearing (identify with Docket number): Hearing Clerk, Office of General Counsel (GC-1), Room 6-62, Parklawn Building.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-5), Bureau of Drugs.

Requests for NAS-NRC report: Press Relations Office (CE-200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: May 17, 1971.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.71-8557 Filed 6-17-71;8:46 am]

NDA 84-902

AF 27-736

Alcon Laboratories, Inc.
Attention: Mr. Richard A. Hamer
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

SEP 30 1975

Gentlemen:

Reference is made to your abbreviated new drug application dated September 9, 1975, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promethacon Supprettes (promethazine hydrochloride suppositories), 50 mg.

We have completed the review of this abbreviated new drug application and have the following comments:

1. Submit twelve copies of the final printed carton and insert labeling identical in content to the drafts.

2. Submit the proposed immediate container labeling.

3. Specify the composition of the food coloring, or the appropriate Drug Master File referral from the manufacturer.

4. Submit samples of the drug dosage form with the results of all tests performed.

Please let us have your response promptly.

Sincerely yours,

/S/ 9/30/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO
Dup 9/29/75
HFD-530 HFD-614 HFD-616
JRCarr/JMeyer/JTaylor 9-23-75 9/29/75
R/D init. JMeyer/MSeife 9-26-75
Final typing/wlb/9=26=75
Rev w/f

/S/ 9/29/75

Pink

NDA 84-901
84-902
AF 27-736

OCT 23 1975

Alcon Laboratories, Inc.
Attention: Mr. Richard Hamar
P.O. Box 1959
6201 South Freeway
Fort Worth, TX 76101

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promethacon Suprettes (Promethazine Hydrochloride Suppositories).

We acknowledge receipt of your communication dated October 7, 1975, which contained preliminary stability data and make a commitment to submit additional data as it becomes available.

Reference is also made to our communication dated September 30, 1975.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the information requested per our above-referenced communication is required.

Please let us have your response promptly.

Sincerely yours,

/S/ 10/23/75

Melvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO

dup
HFD-614 HFD-616
JLMeyer/JTaylor 10/22/75
R/D init. JLMeyer, MSeife 10/21/75
Final typing bho 10/21/75
Rev. w/f

/S/ 10/22/75

[redacted]

Ark

Alcon Laboratories, Inc.
Attention: Mr. Richard A. Ruger
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

DEC 18 1975

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Promethazine Suppository, 25 mg. (promethazine hydrochloride suppositories).

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

> The relative rates at which promethazine suppositories dissolve in diverse test mediums have been shown to be related bioavailability in humans; accordingly, this study cannot be recommended as a demonstration of bioequivalence of the two products.

If you disagree with the above comments, or wish to discuss this matter in greater detail, we shall be glad to meet with you for that purpose.

Sincerely yours,

[redacted]
Marvin Seife, M.D.
Director
Division of Over-the-Counter Monograph
Office of Drug Evaluation
Bureau of Drugs

cc:
DL
HFD-530-Meyer
HFD-520 Murdock
HSeife/krlb/12-16-75

NDA 84-902

FEB 24 1976

Alcon Laboratories, Inc.
Attention: Mr. Richard Hammer
6201 South Freeway
Fort Worth, TX 76101

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promethazine Hydrochloride Suppositories, 50 mg.

We acknowledge receipt of your communications dated December 5, and 15, 1976.

We have completed the review of this abbreviated new drug application and have the following comments:

1. Submit twelve copies of the final printed immediate container labeling.
2. Adequate data to assure the biologic availability of the drug in the form in which it is to be marketed are required. It is suggested that the proposed protocol be submitted for review prior to initiating any actual studies.

Please let us have your response promptly.

Sincerely yours,

/S/ 2/24/76

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO
dup 2/23/76
HFD-614 HFD-616
JRCarr/JLMeyer/JTaylor 2/23/76
R/D init. JLMeyer, MSeife 2/20/76
Final typing bho 2/23/76
Rev. w/f

/S/ 2/23/76

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 84-901, 84-902

Alcon Laboratories, Inc.
Attention: Mr. H.A. Whissen
Box 1959
Fort Worth, TX 76101

NOV 04 1976

Gentlemen:

Product: Promethazine Oral

In accord with Administration guidelines, the labeling for the above drug dosage form has been updated.

We call to your attention the accompanying material and request revision of your package insert - at the time of the next printing.

Please submit twelve copies of the revised labeling within 180 days.

Sincerely yours,

/S/ 11/4/76

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure:
Labeling guidelines

cc:
ANDA (orig dup.)
MSeife/wlb/11-4-76

APR 3 1979

NDA 84-901
NDA 84-902

Alcon Laboratories, Inc.
Attention: Mr. Richard A. Hamer
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

Gentlemen:

Reference is made to the letter submitted on your behalf by Kleinfeld, Kaplan and Becker, requesting deferral of bioavailability studies for Promethacon Suppettes (promethazine hydrochloride suppositories), 25 mg. and 50 mg.

The request was reviewed by our Division of Biopharmaceutics and they have the following comments:

"The Division of Biopharmaceutics cannot grant this deferral and cannot recommend approval of the application under 320.21(c) lacking proof of bioequivalence to the reference drug, i.e., Phenergan Rectal Suppositories (Wyeth).

The firm should be advised that they must either demonstrate the bioequivalence of their product, i.e., Promethacon Suppositories to Wyeth's Phenergan Suppositories or perform a small clinical trial to establish the safety and efficacy of their product.

The firm should be advised that although it is not mandated, it is highly recommended that they include Phenergan oral tablet as an additional reference standard. In the absence of such a standard, Dr. Crout, at a February 8, 1979 meeting, recommended that a box warning be included in the labeling stating: "Bioequivalence between the oral tablet and suppository has not been established".

Basis of Recommendation:

1. The Division of Biopharmaceutics has ample documentation of bioavailability/bioequivalence problems with suppository drug products.

2. In the absence of bioequivalence data, the Division has no assurance that labeling (dosage administration) is appropriate for this product. Due to the clinical use of this product it is necessary to demonstrate bioequivalence to the reference product in lieu of a clinical trial to assure therapeutic equivalence.

3. An analytical method to measure Promethazine in plasma has been reported in the Journal of Pharmacy and Pharmacology, 28 Suppl. 56P (1976). The Division of Biopharmaceutics has contacted

who stated that the method was reproducible, sensitive and linear."

Sincerely yours,

/S/ 4/2/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO DUP HFD-614
HFD-520 Bio
HFD-530 Meyer
MSeife/wlh/4-2-79
bio letter

1979

NDA 84-981
NDA 84-982

Alcon Laboratories, Inc.
Attention: Mr. Roger Metzler
P.O. Box 1958
Fort Worth, TX 76101

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Promethacon Suppettes (promethazine hydrochloride suppositories) 25 mg. and 50 mg.

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. The total volume of blood collected over the three-week test period is estimated to be 540 ml.per subject. Again, this is in excess of the 450 ml. per 1 month per subject specification imposed by this Agency. The volume of the sample collection at 30 minutes could be substituted for collections at 20 and 40 minutes. This would reduce the total volume collected per subject to 495 ml.

2. A sample (suppositories) of the same lot as used in the bioavailability study should be forwarded to

Ms. Angela C. Gresham, R.Ph.
FDA, Bureau of Drugs
Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, MD 20857

3. The analyst must demonstrate that the method for promethazine is sensitive, specific, and reliable when used for pharmacokinetic studies following the rectal administration of suppository preparations.

RECOMMENDATIONS: The protocol is approved provided the firm incorporates comments 1 and 2 into the study design and submits the data described in comment 3 at a later date."

cc: DAL-DO DUP
HFD-614 HFD-520 HFD-530
MSeffe/wh/11-5-79
bio

Sincerely yours,

11/5/79

Melvin Seffe, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

FEB 4 1981

NDA 84-902

Alcon Laboratories, Inc.
Attention: Mr. Richard A. Hamer
P.O. Box 1959
Fort Worth, TX 76101

Gentlemen:

Reference is made to the bioavailability study you submitted on September 5, 1980 for Promethazine Hydrochloride Suppositories, 50 mg.

The study has been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. The report stated that spiked serum samples and drug-free serum yielded unidentified peaks, one on the shoulder of the promethazine peak. Indicate whether the promethazine concentration reported reflects any within or between-subject variation in this unidentified peak. For example, did the analyst subtract a blank value from unknown sample values for the same subject?

2. State the decision rules for reporting a sample promethazine concentration as zero (0).

3. Show the extent to which the promethazine-trichloroethylchloroformate product was characterized.

4. The study shows large within subject variation. For example, when each subject was used as his own control, C_{max} following administration of the Alcon suppositories was 1.1 times that following Phenergan Syrup Fortis. However, less than 70% (8/14) of the subjects were in the range (proposed Phenothiazine Bioequivalence Requirements, Federal Register, p.56838, August 26, 1980). Only 4 of 14 subjects were in the range when subjects were evaluated for the relative bioavailability of the test suppositories (Alcon) and reference solution.

5. Given that the assay method is valid, the study shows that the Alcon suppositories are 1.4 times as bioavailable as the Phenergan Syrup. Further, 7 of 14 subjects exhibited a relative bioavailability $\geq$ 1.4. These results indicate that the Alcon suppositories are certainly more bioavailable than the innovator's suppositories; they were 0.9 times as bioavailable as the syrup.

RECOMMENDATIONS: The firm is informed of the above comments. The submission is incomplete due to the following deficiencies:

DEFICIENCIES:

1

Sincerely yours,

/S/ 2/3/81

Martin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO DUP HFD-530
HFD-520
MSeife/wh/2-3-81
bio

JUL 27 1981

NDA 84-902

Alcon Laboratories, Inc.
Attention: Roger Q. Metzler
6201 South Freeway
P.O. Box 1959
Fort Worth, TX 76101

Gentlemen:

Reference is made to the bioavailability study you submitted for Promethazine Suppositories, 50 mg.

The study has been reviewed by your Division of Biopharmaceutics and they have the following comments:

"RECOMMENDATION

The bioavailability study (submission dated: September 5, 1980) conducted by [redacted] has been found acceptable to the Division of Biopharmaceutics as partial fulfillment of the Bioavailability/Bioequivalence Requirements. The Division of Biopharmaceutics has determined that your application has fulfilled all the necessary elements of the Bioavailability/Bioequivalence Requirement."

Sincerely yours,

/S/

[redacted], M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

7/27/81

cc:
DAL-DO
HFD-520
HFD-530
MSeife/7/24/81
pb/7/24/81
Bio

AUG 28 1981

NDA 84-902

Alcon Laboratories, Inc.
Attention: Roger Matzler
P.O. Box 1959
Fort Worth, TX 76101

Gentlemen:

Reference is made to the dissolution data you submitted for Promethacon (Promethazine Hydrochloride) Suppositories, 50 mg.

The data have been reviewed by our Division of Biopharmaceutics and they have the following comments:

"The firm is informed that the Agency has no dissolution test requirement for promethazine suppositories. However, the Agency encourages the firm to develop dissolution test methodology and specifications in water and/or buffer which resemble biological fluids.

RECOMMENDATIONS: The Dissolution Study No. PRZ 7750140 submitted July 7, 1981 (original submission dated 10-31-75) and conducted by the

has been reviewed by the Division of Biopharmaceutics.

The Division of Biopharmaceutics has determined that your application has fulfilled all the necessary elements of the Bioavailability/Bioequivalence Requirement."

Sincerely yours,

/S/

8/27/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DAL-DO DUP
HFD-530
HFD-520
HFD-614
MSeife/wh/8-27-81
bio

10/1/81
THIS SUBMITTED FPL IS SATISFACTORY.
M.S.

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

September 1, 1981

Marvin Seife, M.D.
Director, Division of Generic
Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

FPL

Re: Promethacon™ Supprettes™ 50 mg
(Promethazine HCl Suppositories)
ANDA 84-902

Dear Dr. Seife:

I am forwarding twelve (12) copies of our final printed package insert as discussed during our telephone conversation of August 17, 1981.

Sincerely,

Roger Q. Metzler

Roger Q. Metzler
Director, Regulatory Affairs

RQM:cr
Attachments

RECEIVED
SEP 3 1981
GENERIC DRUGS

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

August 17, 1981

ORIGINAL

NEW CORRES

Marvin Seife, M.D.
Director, Division of Generic Drug
Monographs
Office of Drug Monographs
(HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

NAF
8/24/81

Re: Promethacon™ Supprettes™ 50 mg
(Promethazine HCl Suppositories)
ANDA 84-902

Dear Dr. Seife:

We are forwarding, under separate cover, a sample consisting of 240 Promethazine HCl, 50 mg Suppositories per your request of June 25, 1981. This sample is labeled with lot code PB-077-81. A copy of our certificate of analysis for this lot is attached to this letter.

Sincerely,

Roger Q. Metzler

Roger Q. Metzler
Director, Regulatory Affairs

RQM/cr
Attachment

RECEIVED
AUG 19 1981
GENERIC DRUGS

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101
Phone (817) 293-0450 Telex 75-8320

June 25, 1981

HAND DELIVERED

BIOAVAILABILITY MATERIAL
RESUBMISSION
NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director, Division of Generic Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Re: Promethacon™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-902

Dear Dr. Seife:

Reference is made to your letter of February 4, 1981 advising us of the comments and deficiencies noted by the Division of Biopharmaceutics following their review of our bioavailability studies submitted on September 3, 1980. Please find attached, our response to these comments and deficiencies.

Each comment or deficiency cited in your letter is set forth on a separate page with our response following. In those cases where additional material is being submitted in support of our response, this material is described in our response and included on the following pages.

Sincerely Yours,

Roger Q. Metzler

Roger Q. Metzler
Director of Regulatory Affairs

RQM:pr
Attachments

RECEIVED
JUN 25 1981
GENERIC DRUGS

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY P.O. BOX 1959, FORT WORTH TEXAS 76101
Phone (817) 293-0450 Telex 75-8320

answered 2/4/81 noted rej 9/9/82

September 3, 1980

HAND DELIVERED

NDA ORIG AMENDMENT

BIOAVAILABILITY MATERIAL

Marvin Seife, M.D.
Director, Division of Generic
Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

RE: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-902

Dear Dr. Seife:

Reference is made to your letter of September 30, 1975, advising us of the completion of your review of the subject ANDAs. In addition, please reference your subsequent letters of December 18, 1975, February 24, 1976 and April 3, 1979, requesting demonstration of in-vivo bioequivalence of our product to Wyeth's Phenergan® Suppositories.

At this time, we are pleased to submit, in triplicate, an Amendment to ANDAs 84-901 and 84-902 providing the results of our recently completed bioavailability studies with the subject products in human volunteers.

This submission consists of three volumes (3) as follows:

1. Volume I provides the following revisions and additions to information contained in the original submission and subsequent amendments:

   a. Part 4, pages 1-8: The package insert has been revised to include information obtained from the bioavailability study. Format has been revised in accordance with new 21CFR §201.56 (44 F.R., June 26, 1979).

   b. Part 7 and 8v, pages 9-36: provides for an alternate assay method for promethazine hydrochloride in the finished dosage form. This alternate assay method may be used in stability studies and as a release assay.

c. Part 7 and 8v, pages 36-58: provides updated stability data justifying a 24-month expiration date. We commit to perform stability testing on the first three (3) production batches and submit results periodically. We hereby agree to promptly withdraw from the market any lots that are shown to become subpotent.

d. Part 7 and 8v, pages 59-65: provides a Bibliography of references.

2. Volume II provides the results of our bioavailability study with Promethacon™ Supprettes™, Phenergan Suppositories (Wyeth), and oral Phenergan Syrup Fortis (Wyeth) in human volunteers. The results of this study clearly demonstrates that the bioavailability of Promethacon™ Supprettes™ is superior to that of Phenergan Suppositories and is, in fact, equivalent to that of oral Phenergan Syrup Fortis administered in equivalent doses. Analytical methodology for determination of promethazine hydrochloride in serum is also included.

3. Volume III provides Investigators Curriculum Vitae, Clinical Laboratory Reports and Case Report Forms for individual subjects participating in the bioavailability study.

As you requested, we are also submitting a fourth (desk) copy of Volumes II and III to facilitate review of the bioavailability data by the Division of Biopharmaceutics.

We trust that the information submitted will enable you to complete a satisfactory review of these applications.

Sincerely,

Roger Q. Metzler

Roger Q. Metzler
Director of Regulatory Affairs

RQM:lg
Enclosures

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1[illegible]9, FORT [illegible]RTH, TEXAS 76101

September 5, 1979

Protocol in
84-901
Jacket

Certified Mail #995704
Return Receipt Requested

RESUBMISSION

NDA ORIG AMENDMENT

Marvin Seife, M. D.
Director, Division of Generic Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON® Supprettes™
25 mg and 50 mg (Promethazine Hydrochloride Suppositories)
ANDA 84-901 and 84-902, September 9, 1975

Dear Mr. Seife:

Reference is made to our letter of June 20, 1979, submitting a proposed protocol for a bioavailability comparison of 50 mg rectal and oral doses of promethazine HCl. The subject protocol was reviewed during a meeting with Drs. Skelly, Rotenberg, Purich and Dighe of the Division of Biopharmaceutics on June 20, 1979, and several revisions were suggested and discussed. During a telephone conversation on August 31, 1979 with Dr. Frank Pelsor, Division of Biopharmaceutics, he reiterated some of the comments made during the June 20, 1979 meeting and requested that we not begin the study until the protocol was revised to accomodate those suggestions.

Accordingly, we are pleased to submit herewith, in triplicate, a revised protocol for a bioavailability comparison of 50 mg rectal dose of promethazine HCl (Phenergan-Wyeth and Promethacon-Alcon) and a 50 mg oral dose (Phenergan Syrup Fortis-Wyeth) in 24 human volunteers utilizing a three-way crossover design. The revised protocol incorporates most of the suggestions made by the Division of Biopharmaceutics staff.

This revised protocol has been reviewed and approved by the investigators and is currently awaiting approval by the Institutional Review Board of [illegible] We propose to begin the study as soon as the protocol receives IRB approval, anticipated in October, 1979.

RECEIVED
SEP 10 1979
GENERIC DRUG

Sincerely yours,

Roger Metzler

Roger Metzler
Manager of Regulatory Compliance

RM:aj

cc: Dr. Frank Pelsor

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101
Phone (817) 293-0450 Telex 75-8320

RICHARD A. HAMER
Manager of Regulatory Compliance

The communication dated 9/5/79 from Alcon supercedes this letter & has been responded to in our letter dated 11/6/79.

June 20, 1979

HAND-DELIVERED

NDA ORIG AMENDMENT

NAI RCP 12/20/79

Marvin Seife, M.D.
Director, Division of Generic Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™
25 mg and 50 mg (Promethazine Hydrochloride Suppositories)
ANDA 84-901 and 84-902, September 9, 1975

Dear Dr. Seife:

Reference is made to your letter of April 3, 1979, stating the comments of the Division of Biopharmaceutics regarding Alcon's request for deferral of bioavailability studies for Promethacon Supprettes (promethazine hydrochloride suppositories) 25 mg and 50 mg, pending development of suitable assay methodology.

As indicated in our letter of February 8, 1979, Alcon has, since June, 1976, actively pursued development of methodology for measuring the biologic availability of promethazine. These efforts have recently come to fruition with development of a method which is felt to be suitable for determining promethazine levels in plasma. The issue of deferral of bioavailability studies for the subject products has therefore become moot at the present time.

Submitted herewith for review, are triplicate copies of a proposed protocol for a bioavailability comparison of 50 mg rectal doses of promethazine HCl (Phenergan-Wyeth and Promethacon-Alcon) and a 50 mg oral dose (Phenergan Syrup Fortis-Wyeth) in 12 human volunteers utilizing a three-way crossover design. Proposed methodology for measuring plasma levels of promethazine is also included in this submission.

RECEIVED
JUN 20 1979
GENERIC DRUGS

Our current plan calls for the initiation of the bioavailability study at on or about July 16, 1979. While we recognize this to be a fairly tight schedule, we hope that the Division of Biopharmaceutics will be in a position to comment on the adequacy of the proposed protocol and assay methodology, as it relates to approval of our pending ANDAs, prior to that date.

Your cooperation is this matter is very much appreciated.

Sincerely yours,

Richard A. Hamer

RAH:cob
Enclosures.

VINCENT A. KLEINFELD
ALAN H. KAPLAN
ROBERT H. BECKER
THOMAS O. HENTELEFF
RICHARD S. MOREY
PETER O. SAFIR
F. KAID BENFIELD
GLENN E. DAVIS
MARC H. SHAPIRO
CHARLES H. BARR

LAW OFFICES
KLEINFELD, KAPLAN AND BECKER
1200 SEVENTEENTH STREET, N. W.
WASHINGTON, D. C. 20036

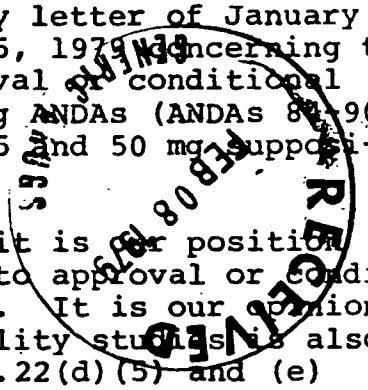
TELEPHONE
(202) 659-2155

February 8, 1979

Bernard E. Cabana, Ph.D.
(HFD-520)
Division of Biopharmaceutics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Cabana:

This is in further reference to my letter of January 29, 1979, and our meeting of February 5, 1979 concerning the bioavailability requirements for approval or conditional approval of Alcon Laboratories' pending ANDAs (ANDAs 84-901 and 84-902) for its promethazine HCl 25 and 50 mg. suppositories ("Promethacon").



As discussed during our meeting, it is our position that these pending ANDAs are entitled to approval or conditional approval under 21 CFR 320.21(c). It is our opinion that a deferral of in vivo bioavailability studies is also justified by application of 21 CFR 320.22(d)(5) and (e) individually and concurrently.

These applications satisfy the conditions enumerated in 21 CFR 320.21(c) for deferring the requirement for evidence of in vivo bioavailability or information justifying a waiver of in vivo bioavailability data in that they were under review on July 7, 1977 and, except for the submission of final printed labeling and evidence demonstrating in vivo bioavailability, the applications are approvable (see Exhibits A, B & C). It has always been, and continues to be, Alcon's position that when an assay methodology for measuring promethazine in biological fluids is developed which is acceptable to the FDA,*/ it will promptly begin an in vivo bioavailability study, under a mutually agreed upon protocol,

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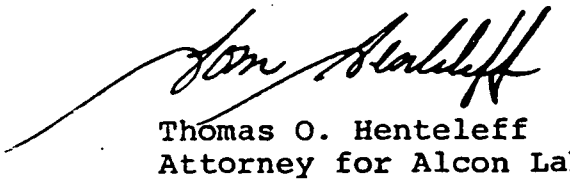
*/ As pointed out in our January 29, 1979 letter (a copy of which is attached as Exhibit D), Alcon has actively, but as yet unsuccesfully, sought to develop methodology for measuring the biologic availability of promethazine. A summary of Alcon's efforts in this continuing endeavor is attached hereto as Exhibit E.

and submit to FDA, as a supplement to its ANDAs, the data generated from these studies. Accordingly, in order for FDA to be in a position to immediately grant a conditional approval for its pending ANDAs, Alcon hereby agrees to conduct in vivo bioavailablity studies and submit the results of the studies to FDA within 180 days from the date a study protocol, including assay methodology, is accepted by FDA as being adequate. A proposed protocol, absent the methodology used for determining in vivo biologic availability, will shortly be submitted to FDA with the objective that FDA and Alcon can promptly agree as to the adequacy of the protocol so that upon agreement of a methodology for determining in vivo biologic availability the study can immediately be initiated and the 180 day clock started.

In conclusion, it is respectfully submitted that FDA's bioavailability regulations, as well as the policy objectives underlying the ANDA system, mandate that the pending ANDAs for Alcon's promethazine preparations be approved or conditionally approved. I will contact your office in two weeks in order to ascertain the Agency's position with respect to the deferral of in vivo bioavailability data and the status of the ANDAs.

Sincerely,



Thomas O. Henteleff
Attorney for Alcon Laboratories

cc: Dr. Marvin Seife

ORIG

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P. O. BOX 1959, FORT WORTH, TEXAS 76101

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

ORIG NEW CORRES

(Items in 84901)

January 20, 1976

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Marvin Seife, M. D.
Director, Division of Generic Drug Monographs
Office of Drug Monographs, HFD-530 Room 16-72
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™ 25 mg and 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-901 and 84-902, dated September 9, 1975

Dear Dr. Seife:

This is to confirm our meeting of January 8, 1976, with the Division of Generic Drug Monographs (represented by you and Dr. Barzilai) and the Division of Biopharmaceutics (represented by Drs. Skelly and Murdock) to discuss the question raised in your letter dated December 18, 1975, with respect to the in vitro dissolution studies contained in the above-referenced applications.

Since Drs. Skelly and Murdock raised certain additional issues during this meeting which were not included in your December 18 letter, and which, in our opinion, are extraneous to the approval of these applications, we take this opportunity to summarize our understanding of the results of this meeting and to reiterate our position on the various issues raised.

Our applications were submitted on the basis that no methodology was available to permit the assay of promethazine hydrochloride in biological fluids and, therefore, no in vivo bioavailability studies could be performed with these products (or other marketed promethazine dosage forms). In

lieu of such in vivo studies, comparative in vitro dissolution studies which, in our opinion, constitute adequate data to assure the biologic availability of the drug products were included in the applications. Recognizing that, ultimately, correlation of in vivo and in vitro data would be necessary, we agreed to perform in vivo bioavailability studies with these products when the necessary methodology became available.

The above conditions were described in both the applications and our letters of transmittal dated September 9, 1975. We submit that these conditions hold true today and that, at the present time, no specific methodology is available for assay of promethazine hydrochloride in biological fluids. While Drs. Skelly and Murdock agreed that no specific methodology is available at this time, they suggested that such methodology could be developed. We do not argue the contention that a specific, reliable assay method may eventually become available and we have made a clear commitment to perform in vivo bioavailability studies with our products at that time. Indeed, Alcon had undertaken some preliminary studies to explore the possibilities of developing such as assay. The fact remains, however, that a specific, reliable in vivo assay method is not available at this time, nor are we in a position to project if and when such a method will become available.

We consider the issue of potential development of an in vivo assay method for promethazine hydrochloride to be academic insofar as it relates to the approval of our applications. We take strong issue with the inference made by the representatives of the Division of Biopharmaceutics that Alcon should undertake the burden of developing an assay method as a prerequisite for approval of these applications, and submit that such a "requirement" has no basis within the context of the Federal Food, Drug and Cosmetic Act and the regulations issued pursuant thereto.

Abbreviated new drug applications for oral dosage forms of promethazine hydrochloride have in the past been approved by the Agency on the basis of in vitro data in the absence of specific in vivo methodology. Promethazine hydrochloride is certainly not unique in this regard; applications for other DESI-reviewed drug products have in the past been approved under similar circumstances. The suggestion that Alcon first develop specific in vivo methodology in order to perform bioavailability studies therefore constitutes an unprecedented change in Agency policy. Furthermore, such a policy

would constitute a discriminatory application of the FFDC Act in that it imposes more stringent requirements on Alcon than on the original NDA-holder who currently markets an identical dosage form. We maintain that, in the absence of specific in vivo assay methodology, the in vitro dissolution studies comparing Promethacon with the marketed reference products (Phenergan, Wyeth) constitute, at this time, adequate data to assure the biologic availability of the products.

The second issue raised by Dr. Skelly concerns the inclusion of promethazine hydrochloride suppositories in a June 20, 1975 Federal Register proposal (40 F.R. 26142-26156) requiring submission of a full NDA for this type of product. We submit that the above-referenced proposal was withdrawn on September 22, 1975 (40 F.R. 43531-43533) and no longer represents Agency policy. This issue is therefore considered to be unrelated to the approval of our abbreviated new drug applications.

The third issue discussed (and the sole question raised in your letter of December 18, 1975) concerns the relationship between dissolution studies (in dioxane) and bioavailability in humans since dioxane, unlike water, is not a physiologic medium. It was necessary to use dioxane as the dissolution medium in order to compare Promethacon and Phenergan since the latter product is insoluble in water. However, during the development of this methodology, the dissolution profiles of our (water-soluble) formulations in dioxane were compared to those in water. It was found that the rate of release of promethazine hydrochloride from our formulations decreased significantly when dioxane was used as the dissolution medium. In spite of this retardation, the dissolution profiles of Promethacon 25 mg and 50 mg compare favorably with those of Phenergan 25 mg and 50 mg in the dioxane studies.

Since Drs. Skelly and Murdock were not aware of the fact that data concerning the relative dissolution rates in water and dioxane were contained in our applications, it was unfortunately necessary to conclude the meeting pending further review of the applications by the Division of Biopharmaceutics.

We propose to contact you by telephone on January 27, 1976, to determine the results of this review. If any questions regarding the in vitro dissolution studies remain at that time, we shall be pleased to meet with Dr.

Cabana and his staff on February 3, 1976, to discuss these questions. If, however, the original question regarding the in vitro data has been affirmatively resolved upon completion of this review, we respectfully request that our applications be approved as per your letter of October 23, 1975.

Sincerely,

Richard A. Hamer
Manager of Compliance

RAH:pw

ORIG

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

NDA ORIG AMENDMENT

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

December 15, 1975

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-902, dated September 9, 1975.

Gentlemen:

Reference is made to our discussion on December 5, 1975, at which time objections were raised to the proposed immediate (foil) container labeling for the subject product.

Accordingly, we wish to amend our application at this time to provide for revised labeling of the unit-dose strip package. We propose to use pre-printed foil bearing trade name, potency, generic name and manufacturer's identification. The lot number and expiration date will be printed on the back of each package during the packaging process. Triplicate copies of revised page 1 for Part 4 (consecutive page 3) are enclosed in support of this change. Please add this information to our file.

Sincerely yours,

Richard A. Hamer
Manager of Compliance

RECEIVED
DEC 18 1975

RAH:pw
Enclosure

Alcon

Rec 12/E

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

RESUBMISSION
NDA ORIG AMENDMENT

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

December 5, 1975

HAND CARRY

FPL

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-902, dated September 9, 1975

Gentlemen:

Further to our letter of October 31, 1975, we are pleased to submit herewith the following materials requested in your letter of September 30, 1975:

(1) Twelve (12) copies of the final printed carton and insert labeling identical in content to the drafts;

(2) Twelve (12) strips containing six (6) samples of the drug dosage form each. A Certificate of Analysis (Lot WKB) is attached herewith, and a copy is enclosed with the product samples. Lot WKB represents the first production batch of this product.

(3) The product samples carry (foil) labeling identical in content to the drafts. Each suppository is imprinted: NDC 0991-4020-12; Lot WKB; Exp 11-76.

In addition, we are submitting additional stability data and a proposed expiration date for the product at this time. Triplicate copies of the following revised pages are enclosed:

(a) Part 7 & 8v, Page 10 (Consecutive page 27) - providing for a 12-month expiration date for the product;

(b) Part 7 & 8v, Pages 20 - 24 (Consecutive pages 36.1 - 36.5) - providing for additional stability data (Lot MEG-3) and proposing a 12-month expiration date.

Please add this information to our file.

Additional stability data on Lot MEG-3 will be submitted as it becomes available. The stability of Lot WKB (first production batch), as well as the next two (2) production batches will be closely monitored and results will be submitted periodically. Any lots shown to become subpotent will be promptly withdrawn from the market.

We trust that the information submitted herewith satisfies the requirements stated in your letter of September 30, 1975, and will enable you to reach a final conclusion regarding this application.

Sincerely yours,

Richard A. Hamer
Manager of Compliance

RAH:pw

Enclosures

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

RESUBMISSION
NDA ORIG AMENDMENT

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

October 31, 1975

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

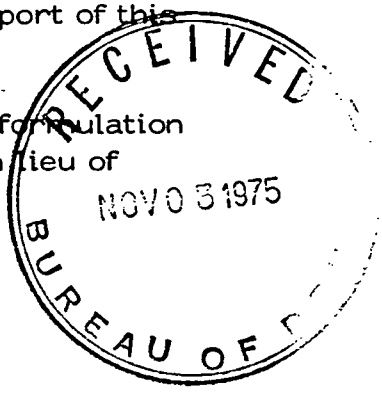
Re: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
ANDA 84-902, dated September 9, 1975

Gentlemen:

We acknowledge receipt of your letters of September 30 and October 23, 1975, advising us of the completion of your review of the subject abbreviated new drug application. The information requested in your letter of September 30 (final printed labeling, foil container labeling, and samples of the finished dosage form) will be submitted within thirty (30) days, as the material becomes available.

With regard to your questions concerning Blue Food Color, we have been unable to obtain the quantitative composition of this material from the supplier. Furthermore, no Drug Master File is currently available for this coloring agent. In view of the above, as well as the uncertain future acceptability of FD&C Red No. 2 contained in Blue Food Color, we propose to substitute FD&C Blue No. 1 for Blue Food Color in the Promethacon 50 mg formulation. Triplicate copies of the following revised pages are enclosed in support of this change:

a) Part 7 & 8i, Page 1 (consecutive page 012) - Revised formulation indicating the presence of FD&C Blue No. 1, 0.025 mg in lieu of Blue Food Color, 0.5 mg per Supprette.



b) Part 7 & 8v, Page 8 (consecutive page 025) - Specifications for FD&C Blue No. 1.

c) Part 4, Page 2 (consecutive page 004) - Revised carton label copy substituting "coloring" for "Blue Food Color."

d) Part 7 & 8vi, Page 1 (consecutive page 037) - Revised manufacturing procedure providing for the addition of FD&C Blue No. 1 to the batch.

We propose to continue our current stability studies on the pilot production batch of Promethacon 50 mg (Lot MEG-3) containing Blue Food Color. Additional stability data, reported on revised pages 21 - 24 for Part 7 & 8v (consecutive pages 36.2 - 36.5), are submitted herewith in triplicate. As agreed previously, the first three (3) production batches (which will contain FD&C Blue No. 1) will be placed on stability and results will be reported periodically. We do not anticipate that the change in coloring ingredients will significantly affect the stability of the product.

At this time, we are also pleased to submit, in triplicate, the results of additional studies confirming the dissolution profile of Promethacon pilot production batches. Additional pages 19a, 19b, 37a, 37b, 37c, 37d, 49a, and 49b (consecutive pages 59.1, 59.2, 77.1, 77.2, 77.3, 77.4, 89.1, and 89.2) are enclosed. Please add this information to our file.

Sincerely yours,

Richard A. Hamer
Manager of Compliance

RAH:pw
Enclosures

Orig

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

NDA ORIG AMENDMENT

October 7, 1975

HAND CARRY

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Supprettes)
ANDA 84-902, dated September 9, 1975

Gentlemen:

Further to our letter of September 9, 1975, we are pleased to submit initial stability results for the subject product. Triplicate copies of Part 7 & 8v, pages 20-24 (consecutive pages 36.1-36.5) are enclosed. For convenience, both the general Table of Contents (consecutive pages 1 and 2) and the Table of Contents for Part 7 & 8v (consecutive page 18) have been revised to reflect the addition of this material. In addition, Part 7 & 8v, page 1 (consecutive page 12) has been corrected to reflect a typical batch size of suppositories (previously stated as Please add this information to our file.

Additional stability data will be submitted as it becomes available.

Sincerely,

Richard A. Hamer
Manager of Compliance

RAH:pw
Enclosures

84-902

Alcon

ALCON LABORATORIES, INC., 6201 SOUTH FREEWAY, P.O. BOX 1959, FORT WORTH, TEXAS 76101

RICHARD A. HAMER
Regulatory Affairs
Webcon Compliance

September 9, 1975

HAND CARRY

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: PROMETHACON™ Supprettes™ 50 mg
(Promethazine Hydrochloride Suppositories)
Abbreviated New Drug Application

Gentlemen:

On behalf of Alcon Laboratories (Puerto Rico), Inc., we are pleased to submit, in triplicate, an Abbreviated New Drug Application for Promethacon Supprettes 50 mg (promethazine hydrochloride suppositories).

Promethazine hydrochloride, in conventional oral and rectal dosage forms, is the subject of DESI Notice 6290, published in the Federal Register dated June 18, 1971 (36 F.R. 11758). This Application is submitted pursuant to, and in conformance with, the conditions specified in DESI 6290.

Under the conditions described in DESI 6290, adequate data to assure the biologic availability of the drug product is to be included in the Submission. At the present time, no methodology is available to permit the assay of promethazine hydrochloride in biological fluids. Therefore, no in vivo bioavailability studies can be performed with this product (or other marketed promethazine dosage forms) at this time. In lieu of such in vivo studies, in vitro dissolution studies have been conducted and the results are included in this Submission.

In the absence of in vivo assay methodology for promethazine hydrochloride, we submit that such in vitro dissolution data constitutes, at this time, adequate data to assure the biologic availability of this product. We recognize that, ultimately, correlation of in vivo and in vitro data will be necessary, and we hereby agree to perform in vivo bioavailability studies with this product when the necessary methodology becomes available.

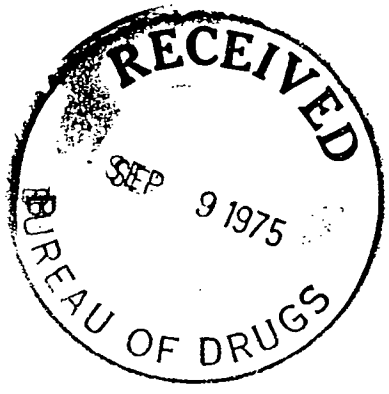
Studies establishing the stability profile of the product are currently in progress, and data will be submitted periodically as it becomes available. The stability of the first three (3) production batches will be closely monitored and results will be submitted periodically. We hereby agree to promptly withdraw from the market any lots that are shown to become subpotent.

Please direct all correspondence concerning this Application to my attention at our Fort Worth office.

Sincerely,

Richard A. Hamer
Manager of Compliance

RAH:pw



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant Alcon Laboratories (Puerto Rico), Inc.

Address P. O. Box 3000, Humacao, Puerto Rico 00661

Date September 9, 1975

Name of new drug Promethacon Supprettes 50 mg (Promethazine HCl Suppositories)

- ☐ Original application (regulation § 130.4).
- ☐ Amendment to original, unapproved application (regulation § 130.7).
- ☒ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Supplement to an approved application (regulation § 130.9).
- ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology. Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

iii. Clinical studies. (Material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW. Food and Drug Administration. Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

Alcon Laboratories (Puerto Rico), Inc.
(Applicant)

Per _____
(Responsible official or agent)

Richard A. Hamer
Manager of Compliance
(Indicate authority)

Alcon Laboratories, Inc., Ft. Worth, Texas

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the nar. and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.