CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 40235

Trade Name Phentolamine Mesylate for Injection USP 5mg/vial

Generic Name Phentolamine Mesylate for Injection USP 5mg/vial

Sponsor Bedford Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40235

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40235

APPROVAL LETTER

ANDA 40-235

MAR 11 1998

Bedford Laboratories
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Phentolamine Mesylate for Injection USP, 5 mg/vial.

Reference is also made to your amendment dated ~~November 17, 1997~~ AUGUST 1, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Phentolamine Mesylate for Injection USP, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Regitine Injection, of Novartis Pharmaceuticals Corporation).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/11/98

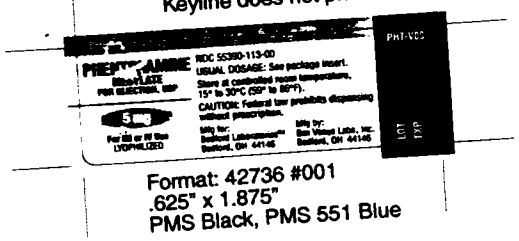
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

FINAL PRINTED LABELING

Keyline does not print

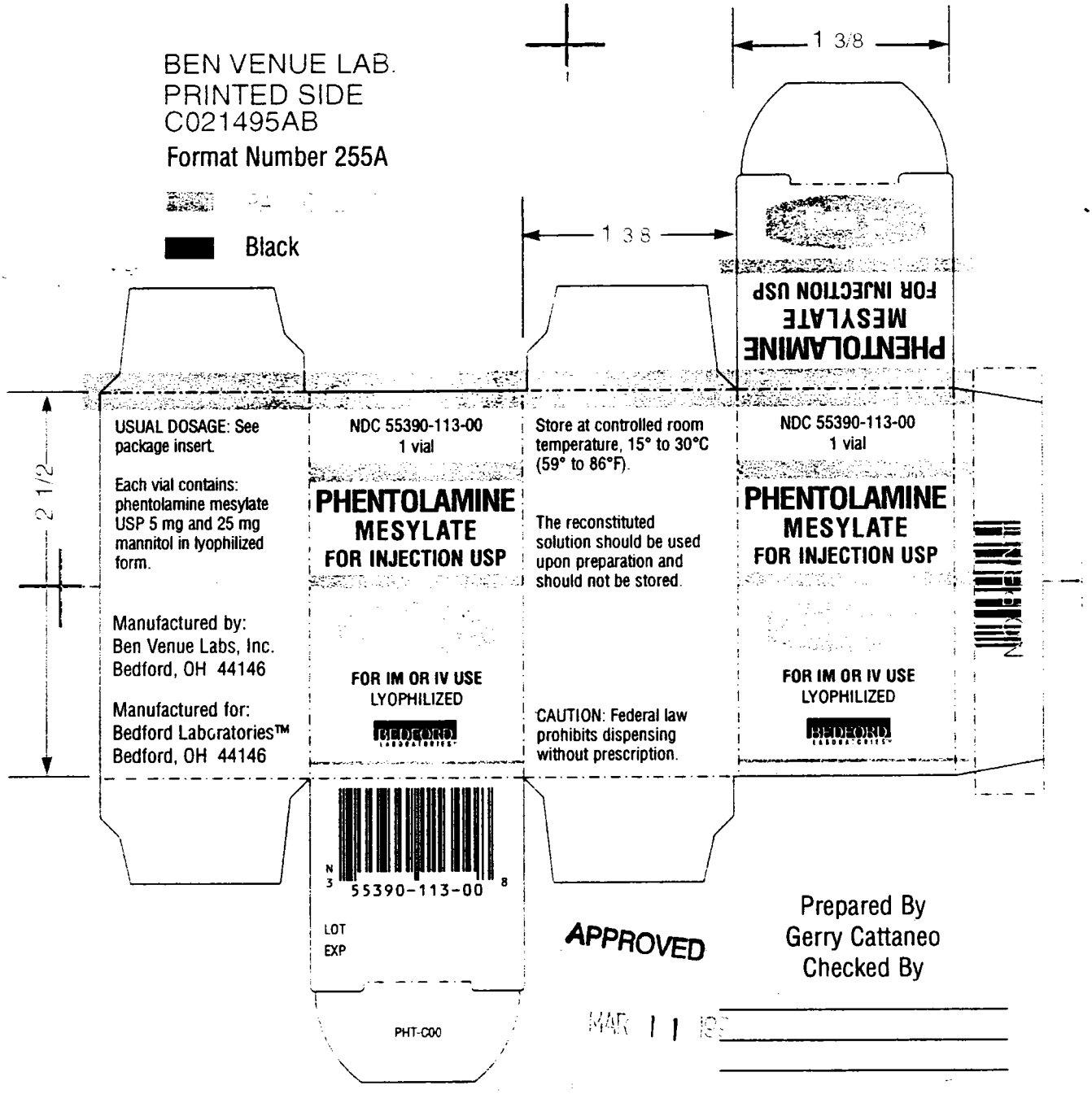


Format: 42736 #001
.625" x 1.875"
PMS Black, PMS 551 Blue

APPROVED

BEN VENUE LAB.
PRINTED SIDE
C021495AB
Format Number 255A

Black



APPROVED

MAR 11 19

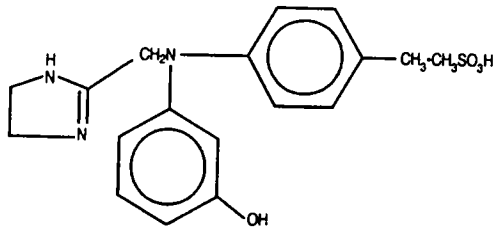
Prepared By
Gerry Cattaneo
Checked By

PHENTOLAMINE MESYLATE FOR INJECTION, USP

DESCRIPTION

Phentolamine Mesylate for Injection USP, is an antihypertensive, available in vials for intravenous and intramuscular administration. Each vial contains phentolamine mesylate USP, 5 mg and mannitol USP, 25 mg in sterile, lyophilized form.

Phentolamine mesylate is *m*-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol monomethanesulfonate (salt), and its structural formula is:



Molecular Formula - $C_{17}H_{19}N_3O \cdot CH_4O_3S$ M.W. - 377.47

Phentolamine mesylate USP is a white or off-white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in alcohol, and slightly soluble in chloroform. It melts at about 178°C.

CLINICAL PHARMACOLOGY

Phentolamine mesylate produces an alpha-adrenergic block of relatively short duration. It also has direct, but less marked, positive inotropic and chronotropic effects on cardiac muscle and vasodilator effects on vascular smooth muscle.

Phentolamine has a half-life in the blood of 19 minutes following intravenous administration. Approximately 13% of a single intravenous dose appears in the urine as unchanged drug.

INDICATIONS AND USAGE

Phentolamine Mesylate for Injection is indicated for the prevention or control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during preoperative preparation and surgical excision.

Phentolamine Mesylate for Injection is indicated for the prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine.

Phentolamine Mesylate for Injection is also indicated for the diagnosis of pheochromocytoma by the phentolamine blocking test.

CONTRAINDICATIONS

Myocardial infarction, history of myocardial infarction, coronary insufficiency, angina, or other evidence suggestive of coronary artery disease; hypersensitivity to phentolamine or related compounds.

WARNINGS

Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the administration of phentolamine, usually in association with marked hypotensive episodes.

For screening tests in patients with hypertension, the generally available urinary assay of catecholamines or other biochemical assays have largely replaced the phentolamine and other pharmacological tests for reasons of accuracy and safety. None of the chemical or pharmacological tests is infallible in the diagnosis of pheochromocytoma. The phentolamine blocking test is not the procedure of choice and should be reserved for cases in which additional confirmatory evidence is necessary and the relative risks involved in conducting the test have been considered.

PRECAUTIONS

General

Tachycardia and cardiac arrhythmias may occur with the use of phentolamine or other alpha-adrenergic blocking agents. When possible, administration of cardiac glycosides should be deferred until cardiac rhythm returns to normal.

Drug Interactions

See **DOSAGE AND ADMINISTRATION. Diagnosis of pheochromocytoma,** *Preparation.*

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies, mutagenicity studies, and fertility studies have not been conducted with phentolamine.

Pregnancy: Teratogenic Effects - Pregnancy Category C

Administration of phentolamine to pregnant rats and mice at oral doses 24 to 30 times the usual daily human dose (based on a 60 kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calcanei and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral doses 60 times the usual daily human dose (based on a 60 kg human), a slightly lower rate of implantation was found in the rat. Phentolamine did not affect embryonic or fetal development in the rabbit at oral doses 20 times the usual daily human dose (based on a 60 kg human). No teratogenic or embryotoxic effects were observed in the rat, mouse, or rabbit studies.

There are no adequate and well-controlled studies in pregnant women. Phentolamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from phentolamine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

See **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

Acute and prolonged hypotensive episodes, tachycardia, and cardiac arrhythmias have been reported. In addition, weakness, dizziness, flushing, orthostatic hypotension, nasal stuffiness, nausea, vomiting, and diarrhea may occur.

OVERDOSAGE

Acute Toxicity

No deaths due to acute poisoning with phentolamine have been reported.

Oral LD_{50}'s (mg/kg): mice, 1000; rats, 1250.

Signs and Symptoms

Overdosage with phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, pupillary contraction, visual disturbances; nausea, vomiting, diarrhea; hypoglycemia.

Treatment

There is no specific antidote.

A decrease in blood pressure to dangerous levels or other evidence of shocklike conditions should be treated vigorously and promptly. The patient's legs should be kept raised and a plasma expander should be administered. If necessary, intravenous infusion or norepinephrine, titrated to maintain blood pressure at the normotensive level, and all available supportive measures should be included. Epinephrine should not be used, since it may cause a paradoxical reduction in blood pressure.

DOSAGE AND ADMINISTRATION

The reconstituted solution should be used upon preparation and should not be stored.

1. **Prevention or control of hypertensive episodes in the patient with pheochromocytoma.**
   For preoperative reduction of elevated blood pressure, 5 mg of phentolamine mesylate (1 mg for children) is injected intravenously or intramuscularly 1 or 2 hours before surgery, and repeated if necessary.

   During surgery, phentolamine mesylate (5 mg for adults, 1 mg for children) is administered intravenously as indicated, to help prevent or control paroxysms of hypertension, tachycardia, respiratory depression, convulsions, or other effects of epinephrine intoxication. (Postoperatively, norepinephrine may be given to control the hypotension that commonly follows complete removal of a pheochromocytoma.)

2. **Prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine.**
   For Prevention: 10 mg of phentolamine mesylate is added to each liter of solution containing norepinephrine. The pressor effect of norepinephrine is not affected.

   For Treatment: 5 to 10 mg of phentolamine mesylate in 10 mL of saline is injected into the area of extravasation within 12 hours.

3. **Diagnosis of pheochromocytoma - phentolamine blocking test.**
   The test is most reliable in detecting pheochromocytoma in patients with sustained hypertension and least reliable in those with paroxysmal hypertension. False-positive tests may occur in patients with hypertension without pheochromocytoma.

a. Intravenous

Preparation

The **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** sections should be reviewed. Sedatives, analgesics, and all other medications except those that might be deemed essential (such as digitalis and insulin) are withheld for at least 24 hours, and preferably 48 to 72 hours, prior to the test. Antihypertensive drugs are withheld until blood pressure returns to the untreated, hypertensive level. This test is not preformed on a patient who is normotensive.

Procedure

The patient is kept at rest in a supine position throughout the test, preferably in a quiet, darkened room. Injection of phentolamine is delayed until blood pressure is stabilized, as evidenced by blood pressure readings taken every 10 minutes for at least 30 minutes.

Five milligrams of phentolamine mesylate is dissolved in 1 mL of Sterile Water for Injection. The dose for adults is 5 mg; for children, 1 mg.

The syringe needle is inserted into the vein, and injection is delayed until pressor response to venipuncture has subsided.

Phentolamine is injected rapidly. Blood pressure is recorded immediately after injection, at 30-second intervals for the first 3 minutes, and at 60-second intervals for the next 7 minutes.

Interpretation

A positive response, suggestive of pheochromocytoma, is indicated when the blood pressure is reduced more than 35 mm Hg systolic and 25 mm Hg diastolic. A typical positive response is a reduction in pressure of 60 mm Hg systolic and 25 mm Hg diastolic. Usually, maximal effect is evident within 2 minutes after injection. A return to preinjection pressure commonly occurs within 15 to 30 minutes but may occur more rapidly.

If blood pressure decreases to a dangerous level, the patient should be treated as outlined under **OVERDOSAGE.**

A positive response should always be confirmed by other diagnostic procedures, preferably by measurement of urinary catecholamines or their metabolites.

A negative response is indicated when the blood pressure is elevated, unchanged, or reduced less than 35 mm Hg systolic and 25 mm Hg diastolic after injection of phentolamine. A negative response to this test does not exclude the diagnosis of pheochromocytoma, especially in patients with paroxysmal hypertension in whom the incidence of false-negative responses is high.

b. Intramuscular

If the intramuscular test for pheochromocytoma is preferred, preparation is the same as for the intravenous test. Five milligrams of phentolamine mesylate is then dissolved in 1 mL of Sterile Water for Injection. The dose for adults is 5 mg intramuscularly; for children, 3 mg. Blood pressure is recorded every 5 minutes for 30 to 45 minutes following injection. A positive response is indicated when the blood pressure is reduced 35 mm Hg systolic and 25 mm Hg diastolic, or more, within 20 minutes following injection.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Phentolamine Mesylate for Injection USP, 5 mg, for intramuscular or intravenous use, is supplied in a 2 mL vial and individually boxed. **NDC 55390-113-00.**

The reconstituted solution should be used upon preparation and should not be stored.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

Manufactured by:
Ben Venue Laboratories™
Bedford, OH 44146

April 1997

PHT-P00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 40-235

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Robert V. Kasubick
300 Northfield Road
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION
Regitine© Mesylate, 5 mg/vial (Ciba-Geigy Limited)

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Phentolamine Mesylate for Injection, USP

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

9. AMENDMENTS AND OTHER DATES

December 20, 1996	Original submission
February 14, 1997	Filed
April 10, 1997	NA FAX
April 25, 1997	Amendment
August 1, 1997	Additional micro amendment
November 10, 1997	New Correspondence (This Review)

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s) NDA 8278;

13. DOSAGE FORM
Sterile (lyophilized) Powder

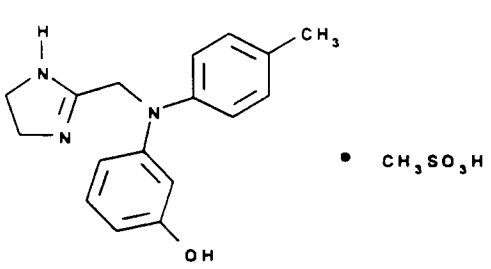
14. POTENCY
5 mg/vial

15. CHEMICAL NAME AND STRUCTURE

3-[[(4,5-Dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino]-phenol monomethanesulfonate (salt)

$C_{17}H_{19}N_3O \cdot CH_4O_3S$ 377.47

CAS [*65-28-1*]



16. RECORDS AND REPORTS N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
February 10, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-620
Microbiologist's Review #3
October 22, 1997

A. 1. **ANDA** 40-235

APPLICANT Bedford Laboratories

2. PRODUCT NAMES: **Phentolamine Mesylate for Injection USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 5 mg/Vial, Sterile Lyophilized Powder in 2 mL Single Dose Vials, Intramuscular and Intravenous

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antihypertensive

B. 1. DATE OF INITIAL SUBMISSION: December 20, 1996

2. DATE OF AMENDMENT: August 1, 1997
Subject of this Review (Received August 4, 1997)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 10/21/97

C. REMARKS: The amendment provides for the for the subject drug product. **The data was not submitted in the April 25, 1997 amendment and was subject of a microbiology deficiency in the Microbiologist's Review #2 dated May 22, 1997.**

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

10/22/97

Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 620 x:wp\microrev\40-235a2
Initialed by R. Patel 10/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

BIOEQUIVALENCE REVIEW(S)

1/1

Smith, S.

ANDA 40-235

Bedford Laboratories
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford OH 44146

MAR 18 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Phentolamine Mesylate USP, 5 mg/Vial.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 12 1997

Phentolamine Mesylate
5 mg/Vial
ANDA # 40-235
Reviewer: Man M. Kochhar
40235W.1296

Bedford Laboratories
Bedford, Ohio
Submission Date:
December 20, 1996

Review of a Waiver Request

The firm has requested a waiver of in vivo bioequivalence study for its phentolamine mesylate injections, 5 mg/vial based upon 21 CFR 320.22 (b)(1).

Comparative Formulation

Ingredients	Bedford mg/vial	Ciba mg/vial
Phentolamine Mesylate	5.0	5.0
Mannitol, USP	25.0	25.0

Deficiency: None

Comments:

1. The formulation of the test product (phentolamine Mesylate) and the innovator product (Regitine; Ciba) is similar in concentration of active and inactive ingredients. Both test and reference products are lyophilized powder in the vial and is reconstituted to 1 mL with water for injection.

2. The dosage form, route of administration (intravenous and intramuscular), strength (5 mg/vial), and labeling of the test product are identical to those of the innovator product, (Regitine). The dosage of test and reference product are same.

3. From the bioequivalence point of view, the waiver of in vivo bioequivalence study requirement should be granted based on 21 CFR 320.22 (b)(1).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories on its lyophilized Phentolamine Mesylate 5mg/vial injections fall under 21 CFR 320.22 (b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of in vivo bioequivalence study for Phentolamine Mesylate (test product) 5 mg/vial injection is granted.

From the bioequivalence point of view, the Division of Bioequivalence deems the test injection of Phentolamine Mesylate 5 mg/vial to be bioequivalent to Regitine 5 mg/vial, manufactured by Ciba Pharmaceuticals.

The firm should be informed of the recommendation.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalece

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 3/6/97

Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: Date: 3/12/97

for Nicholas M. Fleischer, Ph.D
Director
Division of Bioequivalence

MMKochhar/mmk/3-3-97; 40-235

cc: ANDA # 40-235 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhare, Kochhar), Drug File, Division File.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 40-235 Date of Submission: December 20, 1996

Applicant's Name: Bedford Laboratories
Division of Ben Venue Laboratories, Inc.

Established Name: Phentolamine Mesylate for Injection USP, 5 mg

Labeling Deficiencies:

1. CONTAINER

   Revise the storage statement to read "Store at controlled room temperature 15° to 30°C (59° to 86°F).

2. CARTON - 1 vial

   a. Include net quantity statement to read "1 vial".

   b. See the comment under CONTAINER.

3. INSERT

   a. DESCRIPTION

      i. Paragraph 1, sentence 1:

         Phentolamine Mesylate for Injection USP, is an ...

      ii. Paragraph 1, sentence 2:

         ... mesylate USP, 5 mg and mannitol USP, 25 mg in ... [relocation of a "comma" in two places]

      iii. Paragraph 3, sentence 1:

         Delete a "comma" between "mesylate" and "USP".

      iv. Revise the molecular formula to read "$C_{17}H_{19}N_3O \bullet CH_4O_3S$".

      v. Revise the molecular weight to read "377.47" to be in accordance with USP 23.

b. INDICATIONS AND USAGE

i. Revise "Phentolamine mesylate" to read "Phentolamine Mesylate for Injection" at the beginning of the first, second and third paragraphs.

ii. Paragraph 3:

... phentolamine blocking test. [delete "mesylate"]

c. DOSAGE AND ADMINISTRATION

i. Express dosages in "phentolamine mesylate" (not "phentolamine") throughout this section.

ii. 3. Diagnosis of pheochromocytoma - phentolamine blocking test. (*a. Intravenous*)

A) *Preparation*

... , and preferably 48 to 72 hours; ... [rather than "preferable"]

B) *Procedure* - Paragraph 2:

...for children, 1 mg. [add a "comma"]

C) Interpretation

Add a space between mm and Hg throughout this section (e.g., 35 mm Hg).

d. HOW SUPPLIED

i. Revise to read as follows:

Phentolamine Mesylate for Injection USP, 5 mg, for intramuscular or intravenous use, is supplied in a 2 mL vial and individually boxed.

ii. See the comment under CONTAINER.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA **40-235** APPROVAL SUMMARY

DRUG PRODUCT: Phentolamine Mesylate for Injection, USP, 5 mg/vial

FIRM: Bedford Laboratories

DOSAGE FORM: Sterile (lyophilized) Powder

STRENGTH: 5 mg per vial

cGMP STATEMENT/EIR UPDATE STATUS: EER Acceptable Dates, March 19, 1997, and September 19, 1997.

BIO STUDY: Acceptable, Bio Waiver requested. See letter (file date 03/19/97).

VALIDATION: DS and DP are compendial; The District Lab. has found the ANDA method suitable for regulatory control of the Product.

STABILITY: Three months accelerated, 40°C (75% RH), and one month ambient condition, 27.5°C ± 2.5°C, data in the market package size, (5 mg/vial),

aluminum Flip-off seals, provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. All reported data are within specifications as listed. Thus, a 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: Physical appearance, assay

LABELING: APPROVE, Review Date 05/14/1997

STERILIZATION VALIDATION: (IF APPLICABLE): Acceptable, Microbiologist's Review Date October 22, 1997.

SIZE OF BIO BATCH: The bio batch, lot 815-03-0001 vials) is also the test batch (drug substance source, Adequate as of 02/10/98).

SIZE OF STABILITY BATCHES: The Stability Batch is the same as the test batch, ie lot 815-03-0001.

PROPOSED PRODUCTION BATCHES: The proposed production batch size is vials. Master Batch Records for Production Batches were provided.

CHEMIST: **DATE:** 2/10/98

SUPERVISOR: **DATE:**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40235

CORRESPONDENCE

NDTBO
11/14/97

BEDFORD
LABORATORIES™

November 10, 1997

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
NOV 12 1997
GENERIC DRUGS

RE: **ANDA 40-235 - "Minor Amendment"**
PRODUCT: **Phentolamine Mesylate USP, 5 mg/vial**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-235, for Phentolamine Mesylate for Injection USP, 5 mg per vial to remove the deficiencies cited in the letter dated November 3, 1997

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. FDA 356h form is provided in this amendment.

A. Chemistry Deficiencies

11/13/97

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
LABORATORIES™

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are at (216)-232-3320, ext. 333 (direct), (216) 232-2772 (fax).

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

August 1, 1997

AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 40-235 - "Follow-up Commitment"
PRODUCT: Phentolamine Mesylate for Injection USP, 5 mg/vial

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-235, for Phentolamine Mesylate for Injection USP, 5 mg per vial to fulfil the commitment that we have made in our last response dated April 25, 1997.

This is in regard to the response to our Microbiological deficiency concerning for Phentolamine Mesylate for Injection drug product. The study has been completed and satisfactory results were obtained. A copy of the report is provided in this amendment for your review.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216)-232-3320, ext. 218.

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
AUG 04 1997
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2772

BEDFORD
LABORATORIES™

April 25, 1997

NDA ORIG AMENDMENT
NAC FPL

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 40-235 - "Major Amendment"**
PRODUCT: **Phentolamine Mesylate USP, 5 mg/vial**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-235, for Phentolamine Mesylate for Injection USP, 5 mg per vial to remove the deficiencies cited in the letter dated April 11, 1997

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Attachment I provides the FDA 356h form.

A. Chemistry Deficiencies

PAGES 2 AND 3 PURGED
CONTAINING TRADE SECRET INFORMATION
CHEMISTRY

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-8743

GENERIC DRUGS

Labeling Deficiencies:

Based on Agency's comments, vial label, carton and package insert labeling have been updated. Side-by-side comparison (annotated) between our proposed draft label (original application) and labeling versus final printed label and labeling is provided in Attachment V. Twelve copies of final printed label and labeling have been provided in the Attachment V.

Microbiology Deficiencies:

are provided in Attachment VI.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216)-232-3320, ext. 218.

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

APR 10

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-235 APPLICANT: Bedford Labs

DRUG PRODUCT: Phentolamine Mesylate USP, 5 mg/vial

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Sincerely yours,

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

The First Generic Review Audit should have been done, but did not come to the Division Director's notice until the 2nd amc review (minor) was ready 10/22/97

Microbiology Comments to be Provided to the Applicant

ANDA: 40-235 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Phentolamine Mesylate for Injection

Microbiology Deficiencies:

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

Rashmikant M. Patel, Ph.D.

Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MAJOR AMENDMENT

APR 10

ANDA/~~AADA~~ 40-235

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

TO: APPLICANT BEDFORD LABS. PHONE 216-232-3320 x218
ATTN: ROBERT KASIBACK FAX 216-232-2772

FROM: JIM WILSON PROJECT MANAGER (301-594-0310)

Dear Sir/~~Madam~~:

This facsimile is in reference to your abbreviated new drug/antibiotic application 40-235 dated 12/20/96, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for PHENTOLAMINE MESYLATE FOR INJECTION, USP

Reference is also made to your amendments dated 2/14/97.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (6 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/[redacted] notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.mjr

ANDA 40-235

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, OH 44146

FEB 14 1997

Dear Sir:

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

NAME OF DRUG: Phentolamine Mesylate for Injection USP, 5 mg/vial

DATE OF APPLICATION: December 20, 1996

DATE OF RECEIPT: December 24, 1996

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

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

Should you have questions concerning this application, contact:

Jim Wilson
Project Manager
(301) 594-0310

Sincerely yours,

Jerry Phillips 2/14/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD
LABORATORIES™

December 20, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application - "Expedited Review Requested"
PRODUCT: Phentolamine Mesylate for Injection, USP, 5mg/vial

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application Phentolamine Mesylate for Injection, USP, 5mg/vial. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Ciba-Geigy Limited, Regitine® Mesylate, 5 mg/vial) as well as copies of the relevant pages of the **Approved Drug Products with Therapeutic Equivalence Evaluations, 16th edition and supplements.**

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of our application (Phentolamine Mesylate for Injection, USP, 5 mg/vial). The drug product is a sterile powder and it's solution is intended solely for intravenous and intramuscular administration and it contains the active ingredient in the same concentration as in the listed drug.

Due to the shortage of the referenced listed drug product in US marketplace, we would like to request the Agency for an expedite review of this application. Based on our marketing group's information, the availability of this product is very minimum. The wholesalers do not have this product in stock. One can receive this referenced listed drug product in very extreme situations only from Novartis directly and may be obtained from their "emergency" stock.

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Three copies of analytical methods which were used to test this product and an analytical method validation package are enclosed separately along with this application.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol, and the package insert are enclosed separately with this application. This drug product was aseptically filled and lyophilized.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (216)-232-3320, ext. 218 (direct) and (216)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.