CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-512

Generic Name:	Pyridostigmine Bromide Tablets USP, 60mg
Sponsor:	Barr Laboratories, Inc.
Approval Date:	October 8, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

APPROVAL LETTER

ANDA 40-512

OCT 8 2003

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Sir:

This is in reference to your abbreviated new drug application dated September 18, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Pyridostigmine Bromide Tablets USP, 60 mg.

Reference is also made to your amendments dated July 24 and September 16, 2003.

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 Pyridostigmine Bromide Tablets USP, 60 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mestinon® Tablets, 60 mg of ICN Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy 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-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 10/8/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

FINAL PRINTED LABELING

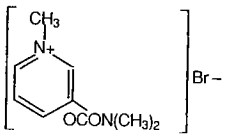
BARR LABORATORIES, INC.

Pyridostigmine Bromide Tablets, USP

Rx only

DESCRIPTION:

Pyridostigmine bromide is an orally active cholinesterase inhibitor. Chemically, pyridostigmine bromide is 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate. Its structural formula is:



$C_9H_{13}BrN_2O_2$ Molecular Weight: 261.12

Pyridostigmine Bromide Tablets contain 60 mg pyridostigmine bromide and contain the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide and stearic acid.

CLINICAL PHARMACOLOGY:

Pyridostigmine inhibits the destruction of acetylcholine by cholinesterase and thereby permits freer transmission of nerve impulses across the neuromuscular junction. Pyridostigmine is an analog of neostigmine (Prostigmin®), but differs from it in certain clinically significant respects; for example, pyridostigmine is characterized by a longer duration of action and fewer gastrointestinal side effects.

INDICATIONS AND USAGE:

Pyridostigmine Bromide Tablets are useful in the treatment of myasthenia gravis.

CONTRAINDICATIONS:

Pyridostigmine bromide tablets are contraindicated in mechanical intestinal or urinary obstruction, and particular caution should be used in its administration to patients with bronchial asthma. Care should be observed in the use of atropine for counteracting side effects, as discussed below.

WARNINGS:

Although failure of patients to show clinical improvement may reflect underdosage, it can also be indicative of overdosage. As is true of all cholinergic drugs, overdosage of pyridostigmine bromide may result in cholinergic crisis, a state characterized by increasing muscle weakness which, through involvement of the muscles of respiration, may lead to death. Myasthenic crisis due to an increase in the severity of the disease is also accompanied by extreme muscle weakness, and thus may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Such differentiation is extremely important, since increases in doses of pyridostigmine bromide or other drugs of this class in the presence of cholinergic crisis or of a refractory or "insensitive" state could have grave consequences. Osserman and Genkins[1] indicate that the differential diagnosis of the two types of crisis may require the use of Tensilon® (edrophonium chloride) as well as clinical judgment. The treatment of the two conditions obviously differs radically. Whereas the presence of myasthenic crisis suggests the need for more intensive anticholinesterase therapy, the diagnosis of cholinergic crisis, according to Osserman and Genkins,[1] calls for the prompt *withdrawal* of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended.

Atropine may also be used to abolish or obtund gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

For detailed information on the management of patients with myasthenia gravis, the physician is referred to one of the excellent reviews such as those by Osserman and Genkins,[2] Grob[3] or Schwab.[4,5]

PRECAUTIONS:

Pyridostigmine is mainly excreted unchanged by the kidney.[6,7,8] Therefore, lower doses may be required in patients with renal disease, and treatment should be based on titration of drug dosage to effect.[6,7]

Pregnancy:

The safety of pyridostigmine during pregnancy or lactation in humans has not been established. Therefore, use of pyridostigmine in women who may become pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

The side effects of pyridostigmine are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine, but for reasons shown in the preceding section the expedient is not without danger. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication.

DOSAGE AND ADMINISTRATION:

Each Pyridostigmine Bromide Tablet contains 60 mg.

Dosage:

The size and frequency of the dosage must be adjusted to the needs of the individual patient.

The average dose is ten 60 mg tablets daily, spaced to provide maximum relief when maximum strength is needed. In severe cases as many as 25 tablets a day may be required, while in mild cases one to six tablets a day may suffice.

Note: For information on a diagnostic test for myasthenia gravis, and for the evaluation and stabilization of therapy, please see product literature on Tensilon® (edrophonium chloride).

HOW SUPPLIED:

Pyridostigmine Bromide Tablets are available as:

60 mg: White, round, flat-faced, beveled-edge tablet. Debossed with b on one side and cross-scored on the other side.
Available in bottle of:
100 NDC 0555-0133-02

Dispense in a tight container as defined in the USP.

PROTECT FROM MOISTURE.

Store at 20-25°C (68°-77°F) [See USP Controlled Room Temperature].

REFERENCES:

1. Osserman KE, Genkins G. Studies in myasthenia gravis: Reduction in mortality rate after crisis. *JAMA.* Jan 1963; 183:97-101.
2. Osserman KE, Genkins G. Studies in myasthenia gravis. *NY State J. Med.* June 1961; 61:2076-2085.
3. Grob D. Myasthenia gravis. A review of pathogenesis and treatment. *Arch Intern Med.* Oct 1961; 108:615-638.
4. Schwab RS. Management of myasthenia gravis. *New Eng J Med.* Mar 1963; 268:596-597.
5. Schwab RS. Management of myasthenia gravis. *New Eng J Med.* Mar 1963; 268:717-719.
6. Cronnelly R, Stanski DR, Miller RD, Sheiner LB. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther.* 1980; 28:No. 1, 78-81.
7. Miller RD. Pharmacodynamics and pharmacokinetics of anticholinesterase. In: Ruegheimer E, Zindler M, ed. *Anaesthesiology.* (Hamburg, Germany: Congress; Sep 14-21, 1980; 222-223.) (Int Congr. No. 538), Amsterdam, Netherlands: Excerpta Medica; 1981.
8. Breyer-Pfaff U, Maier U, Brinkmann AM, Schumm F. Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther.* 1985;5:495-501.

MANUFACTURED BY
BARR LABORATORIES, INC.
Pomona, NY 10970

Revised MAY 2003
BR-133

Each tablet contains 60 mg pyridostigmine bromide.

Usual Dosage: See package brochure.

Dispense with a child-resistant closure in a tight container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

Important - These tablets are hygroscopic.

PROTECT FROM MOISTURE.

Keep in a dry place with desiccant enclosed.

BARR LABORATORIES, INC.
Pomona, NY 10970

R5-03
1120133020101

BARR LABORATORIES, INC.

NDC 0555-**0133**-02

Pyridostigmine Bromide

Tablets, USP

60 mg

Rx only

100 Tablets

SAMPLE

Exp:

Lot:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

CSO LABELING REVIEW(S)

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

ANDA Number: 40-512 Date of Submission: May 21, 2003

Applicant's Name: Barr

Established Name: Pyridostigmine Bromide Tablets USP, 60 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: (100's) FPL submitted on May 21, 2003 (Vol. A2.1, Code R5-03, 1120133020101) is acceptable for approval.
- Professional Package Insert Labeling: FPL submitted on May 21, 2003 (Vol. A2.1, Revised May 2003, 1001330101) is acceptable for approval.
- Revisions needed post-approval: Yes

INSERT (DOSAGE AND ADMINISTRATION)

Revise the first statement to read "Each tablet contains 60 mg pyridostigmine bromide."

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Mestinon
- NDA Number: 9-829
- NDA Drug Name: Mestinon
- NDA Firm: INC Pharmaceutical, Inc.
- Date of Approval of NDA Insert and supplement #: 7/26/01; S-011 — 8th/11 current as of 10/1/03
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by side
- Basis of Approval for the Carton Labeling: NA

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Mestinon Tablets, NDA 9-829/S-009 and S-011, approved July 26, 2001.
2. INACTIVE INGREDIENTS: Consistent with application (see page 07-2 Vol. 1.1)
3. PATENTS/EXCLUSIVITIES: None
4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in tight containers
   - NDA:IMPORTANT: These tablets are hygroscopic. Keep in a dry place with the silical gel enclosed. Store at 59^0 to 86^0F (15^0 to 30^0C)
   - ANDA: Store at 20^0-25^0C(68^0-77^0F)(see USP Controlled Room Temperature).
5. Merck Index indicates that pyridostigmine bromide is a hygroscopic crystal.
6. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in tight containers
   - NDA: Dispense in tight containers as defined in USP/NF
   - ANDA: Dispense in a child-resistant closure in a tight container.
7. PACKAGE CONFIGURATION
   - NDA: Bottles of 100
   - ANDA: Bottles of 100
8. CONTAINER/CLOSURE
   - Container: HDPE
   - Closure: CRC
9. FINISHED DOSAGE FORM
   - NDA:Scored (Quadrisect) Nicole of ICN Pharmaceuticals said that the Mestinon 60 mg tablet has a "cross like" score on one side which can be used to break the tablet into four 15 mg pieces (3/14/02).
   - ANDA: White, round, flat-faced, beveled-edge tablet. Debossed with b over 133 on one side and "cross-scored" on the other side (consistent with application see page 16-44 Vol. 1.5)
10. STORAGE TEMPERATURE STATEMENT

    Barr's Stability Protocol

    Accelerated Storage Condition 40°C ± 2°C/75% ± 5% relative humidity
    Testing Schedule: 1, 2, 3 months
    Long-term Storage Conditions: 25°C ± 2°C/60% ± 5% relative humidity
    Testing Schedule: 0, 3, 6, 9, 12, 18, 24, 36 (tested only under discretion of study sponsor).
    Intermediate Storage Conditions: 30°C ± 2°C/60% ± 5% relative humidity
    Testing Schedule: 1, 2, 3, 6, 9, 12 months

    OGD

    The Office of Generic Drugs accepts stability studies to support room temperature storage at either of the following storage conditions:
    - 25-30 deg C/ambient humidity
    - 25+-2 deg/60%RH (ICH conditions)

    Based on Barr's Stability Protocol, it appears that OGD's standard room temperature storage statement is supported. This will be confirmed in the second chemistry review.

Date of Review: June 5, 2003 Date of Submission: May 21, 2003

Primary Reviewer: Koung Lee Date: 6/13/03

Team Leader: Lillie Golson Date: 6/13/03

cc: ANDA: 40-512
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\BARR\LTRS&REV\40512.AP.labeling
Review

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

ANDA Number: 40-512 Date of Submission: April 4, 2003

Applicant's Name: Barr

Established Name: Pyridostigmine Bromide Tablets USP, 60 mg

Labeling Deficiencies:

1. CONTAINER (100)

   Revise the storage temperature statement to read "Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature)".

2, INSERT

   a. Delete ——— after the molecular formula in the DESCRIPTION section

   b. Replace the section heading ' ——— with "CLINICAL PHARMACOLOGY".

   c. Replace section heading ——————— with "INDICATIONS AND USAGE"

   d. Replace the subsection heading " ——————— with "Pregnancy" and relocate this subsection from WARNINGS to the PRECAUTIONS section before the "Pediatric use" subsection.

   e. Add an "S" to the "PRECAUTION" heading.

   f. DOSAGE AND ADMINISTRATION

      Delete the ' ———————

   g. HOW SUPPLIED

      See CONTAINER comment.

Please revise your labels and labeling as instructed above and submit 12 final printed copies of labels and labeling for a full approval of this application.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Mestinon
- NDA Number: 9-829
- NDA Drug Name: Mestinon
- NDA Firm: INC Pharmaceutical, Inc.
- Date of Approval of NDA Insert and supplement #: 7/26/01; S-011
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by side
- Basis of Approval for the Carton Labeling: NA

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	

Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Mestinon Tablets, NDA 9-829/S-009 and S-011, approved July 26, 2001.

2. INACTIVE INGREDIENTS: Consistent with application (see page 07-2 Vol. 1.1)

3. PATENTS/EXCLUSIVITIES: None

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in tight containers
   - NDA:IMPORTANT: These tablets are hygroscopic. Keep in a dry place with the silical gel enclosed. Store at 59^0 to 86^0F (15^0 to 30^0C)
   - ANDA: Store at controlled room temperature 15^0-30^0C(59^0-86^0F)(seeUSP). Firm is asked to include the following: " IMPORTANT: These tablets are hygroscopic. PROTECT FROM MOISTURE. Keep in a dry place with the dessicant enclosed."

5. Merck Index indicates that pyridostigmine bromide is a hygroscopic crystal.

6. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in tight containers
   - NDA: Dispense in tight containers as defined in USP/NF
   - ANDA: Dispense in a child-resistant closure in a tight container.

7. PACKAGE CONFIGURATION
   - NDA: Bottles of 100
   - ANDA: Bottles of 100 and —

8. CONTAINER/CLOSURE
   - Container: HDPE
   - Closure: 100 = CRC

9. FINISHED DOSAGE FORM
   - NDA:Scored (Quadrisect) Nicole of ICN Pharmaceuticals said that the Mestinon 60 mg tablet has a "cross like" score on one side which can be used to break the tablet into four 15 mg pieces (3/14/02).
   - ANDA: White, round, flat-faced, beveled-edge tablet. Debossed with b over 133 on one side and "cross-scored" on the other side (consistent with application see page 16-44 Vol. 1.5)

10. STORAGE TEMPERATURE STATEMENT

Barr's Stability Protocol
Accelerated Storage Condition 40°C ± 2°C/75% ± 5% relative humidity
Testing Schedule: 1, 2, 3 months
Long-term Storage Conditions: 25°C ± 2°C/60% ± 5% relative humidity
Testing Schedule: 0, 3, 6, 9, 12, 18, 24, 36 (tested only under discretion of study sponsor).
Intermediate Storage Conditions: 30°C ± 2°C/60% ± 5% relative humidity
Testing Schedule: 1, 2, 3, 6, 9, 12 months
OGD
The Office of Generic Drugs accepts stability studies to support room temperature storage at either of the following storage conditions:
- 25-30 deg C/ambient humidity
- 25+-2 deg/60%RH (ICH conditions)

Based on Barr's Stability Protocol, it appears that OGD's standard room temperature storage statement is supported. This will be confirmed in the second chemistry review.

Date of Review: May 1, 2003 Date of Submission: April 4, 2003

Primary Reviewer: Koung Lee Date: 5/7/03

Team Leader: Lillie Golson Date: 5/7/03

cc: ANDA: 40-512
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\BARR\LTRS&REV\40512.NA2.labeling Review

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

ANDA Number: 40-512 Dates of Submission: September 18 and November 1, 2002

Applicant's Name: Barr

Established Name: Pyridostigmine Bromide Tablets USP, 60 mg

Labeling Deficiencies:

1. CONTAINER (100 and ~~—~~,

   For the ~~—~~ count bottle add the following:

   i. **Important** – These tablets are hygroscopic.

   ii. **PROTECT FROM MOISTURE.**

   iii. **Keep in a dry place with desiccant enclosed.**

2. INSERT

   a. Delete ~~—~~ after the molecular formula in the DESCRIPTION section

   b. Replace the section heading ~~—~~ with "CLINICAL PHARMACOLOGY".

   c. Replace section heading ~~—~~ with "INDICATIONS AND USAGE"

   d. Replace the subsection heading ~~—~~ with "Pregnancy" and relocate this subsection from WARNINGS to the PRECAUTIONS section before the "Pediatric use" subsection.

   e. Add an "S" to the "PRECAUTION" heading.

   f. DOSAGE AND ADMINISTRATION

      Delete the ~~—~~

Please revise your labels and labeling as instructed above and submit 12 final printed copies of labels and labeling for a full approval of this application.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Mestinon
- NDA Number: 9-829
- NDA Drug Name: Mestinon
- NDA Firm: INC Pharmaceutical, Inc.
- Date of Approval of NDA Insert and supplement #: 7/26/01; S-011
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by side
- Basis of Approval for the Carton Labeling: NA

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	

Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Mestinon Tablets, NDA 9-829/S-009 and S-011, approved July 26, 2001.

2. INACTIVE INGREDIENTS: Consistent with application (see page 07-2 Vol. 1.1)

3. PATENTS/EXCLUSIVITIES: None

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in tight containers
   - NDA:IMPORTANT: These tablets are hygroscopic. Keep in a dry place with the silical gel enclosed. Store at 59^0 to 86^0F (15^0 to 30^0C)
   - ANDA: Store at controlled room temperature 15^0-30^0C(59^0-86^0F)(seeUSP). Firm is asked to include the following: " IMPORTANT: These tablets are hygroscopic. PROTECT FROM MOISTURE. Keep in a dry place with the dessicant enclosed."

5. Merck Index indicates that pyridostigmine bromide is a hygroscopic crystal.

6. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in tight containers
   - NDA: Dispense in tight containers as defined in USP/NF
   - ANDA: Dispense in a child-resistant closure in a tight container.

7. PACKAGE CONFIGURATION
   - NDA: Bottles of 100
   - ANDA: Bottles of 100 and —

8. CONTAINER/CLOSURE
   - Container: HDPE
   - Closure: 100 = CRC: — = CRC

9. FINISHED DOSAGE FORM
   - NDA:Scored (Quadrisect) Nicole of ICN Pharmaceuticals said that the Mestinon 60 mg tablet has a "cross like" score on one side which can be used to break the tablet into four 15 mg pieces (3/14/02).
   - ANDA: White, round, flat-faced, beveled-edge tablet. Debossed with b over 133 on one side and "cross-scored" on the other side (consistent with application see page 16-44 Vol. 1.5)

Date of Review: February 4, 2003 Date of Submission: 9/18/02 & 11/1/02

Primary Reviewer: Koung Lee C Park for Date: 2/19/03

Team Leader: Lillie Golson Lillie Golson Date: 2/20/03

cc: ANDA: 40-512
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\BARR\LTRS&REV\40512.na.labeling
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

CHEMISTRY REVIEW(S)

ANDA 40-512

Pyridostigmine Bromide Tablets, USP

Barr Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-512

2. REVIEW #1

3. REVIEW DATE:

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents Firm:	Document Date
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002
FDA:	
Telecon Record	29-Oct-2002
Acceptable for filing letter	06-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Barr Laboratories, Inc.
Address:	2 Quaker Road P.O. Box 2900 Pomona, NY 10970
Representative:	Nicholas Tantillo

Telephone: (845) 348-8051

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mestinon
b) Non-Proprietary Name (USAN): Pyridogstimine Bromide Tablets, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Barr Laboratories, Inc. (Barr) proposed ANDA for Pyridostigmine Bromide Tablets USP, 60 mg, is the approved, reference listed drug (RLD) Mestinon® 60 mg, the subject of application NDA #9829, held by ICN Pharmaceutical. The RLD Mestinon ® 60 mg is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," updated as of 11/20/2001 (Electronic Orange Book).

In accordance with Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act, Barr certifies that in their opinion and to the best of their knowledge, the patents which claim for Pyridostigmine Bromide (the drug product or the drug substance that is a component of the drug product) on which investigations, relied upon for this application, were conducted or that claim an approved use of such drug, have all since expired. To the best of Barr's knowledge, Mestinon ® 60 mg is not listed as having any marketing exclusivity under section 505 (j) (4) D) of the Federal Food, Drug, and Cosmetic Act, and is therefore not entitled to a period of marketing exclusivity.

10. PHARMACOL. CATEGORY: Cholinesterase inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pyridostigmine Bromide

3-[[(Dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide. $C_9H_{13}BrN_2O_2$. 261.12. [101-26-8].

17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Deficient	10/24/02	Reviewed by R.Rajagopalan
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/11/02	
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Acceptable	2/5/03	
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 40-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Pyridostigmine Bromide 60 mg, is a non-sterile, USP drug. The active agent in this immediate release dosage form is Pyridostigmine Bromide, an orally active cholinesterase inhibitor (inhibits the destruction of acetylcholine by cholinesterase allowing freer transmission of nerve impulses across the neuromuscular junction.). The approved, reference listed drug is Mestinon® , the subject of application NDA #9829, held by ICN. Barr Laboratories will market the drug product in HDPE bottles of 100's and —

Drug Substances: Pyridostigmine Bromide USP is a white crystalline powder derived from pyridine with the following chemical name/formula/MW: 3-[[(dimethylamino)carbonyl]oxy]-1-methyl-,bromide, C_9H_{13} Br N_2O_2, 261.12. The firm uses the USP tests and specifications to monitor the quality of the drug substance along with in-house tests and specifications for residual solvents and chromatographic purity. The key physicochemical properties monitored for the drug substance that influence batch-to-batch reproducibility are loss on drying and residual solvents.

Formulation and Manufacturing Process: The product formulation, in addition to Pyridostigmine Bromide USP contains Anhydrous Lactose NF, Colloidal Silicon Dioxide NF, and Stearic acid, NF. These inactive ingredients are widely used in the pharmaceutical industry and are not expected to affect the safety and effectiveness of the drug product. The product is manufactured by — process of the —. No inks or dyes are used to imprint the tablets.

The size of the production and biobatch are the same: —Tablets.

Method Validation: Pyridostigmine Bromide 60 mg, is a USP compendial item. Therefore method validation testing by a FDA laboratory is not required.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The following key deficiencies have been noted. The firm should revise the drug substance and drug product release and stability specifications to include all known impurities. Supporting data for the new manufacturing humidity requirements should be provided since approximately half of the exhibit batch was [redacted]. Finally, the failing dissolution results of the drug product under accelerated stability conditions do not support the requested expiration date.

In addition to the above chemistry, manufacturing, and controls issues, the labeling review is pending.

Based on the deficiencies described above, the firm should resolve all of the issues requested.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/

HFD-645/BArnwine

HFD-617/NPark/

C. CC Block

ANDA 40-512
DIV FILE
Field Copy

Redacted 21

Page(s) of trade secret and /or confidential commercial information

ANDA 40-512

Pyridostigmine Bromide Tablets, USP

Barr Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-512

2. REVIEW #2

3. REVIEW DATE: May 16, 2003.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002
FDA:	
Telecon Record	29-Oct-2002
Acceptable for filing letter	06-Nov-2002
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	04-Apr-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Barr Laboratories, Inc.
Address:	2 Quaker Road P.O. Box 2900 Pomona, NY 10970
Representative:	Nicholas Tantillo

Chemistry Review Data Sheet

Telephone: (845) 348-8051

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mestinon
b) Non-Proprietary Name (USAN): Pyridogstimine Bromide Tablets, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Barr Laboratories, Inc. (Barr) proposed ANDA for Pyridostigmine Bromide Tablets USP, 60 mg, is the approved, reference listed drug (RLD) Mestinon® 60 mg, the subject of application NDA #9829, held by ICN Pharmaceutical. The RLD Mestinon ® 60 mg is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," updated as of 11/20/2001 (Electronic Orange Book).

In accordance with Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act, Barr certifies that in their opinion and to the best of their knowledge, the patents which claim for Pyridostigmine Bromide (the drug product or the drug substance that is a component of the drug product) on which investigations, relied upon for this application, were conducted or that claim an approved use of such drug, have all since expired. To the best of Barr's knowledge, Mestinon ® 60 mg is not listed as having any marketing exclusivity under section 505 (j) (4) D) of the Federal Food, Drug, and Cosmetic Act, and is therefore not entitled to a period of marketing exclusivity.

10. PHARMACOL. CATEGORY: Cholinesterase inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pyridostigmine Bromide

3-[[(Dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide. $C_9H_{13}BrN_2O_2$. 261.12. [101-26-8].

17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	2/12/03	Reviewed by R.Rajagopalan
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/11/02	
Methods Validation	N/A		
Labeling	Deficient	5/7/03	Koung Lee
Bioequivalence	Acceptable	2/5/03	Moheb Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 40-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Pyridostigmine Bromide 60 mg, is a non-sterile, USP drug. The active agent in this immediate release dosage form is Pyridostigmine Bromide, an orally active cholinesterase inhibitor (inhibits the destruction of acetylcholine by cholinesterase allowing freer transmission of nerve impulses across the neuromuscular junction.). The approved, reference listed drug is Mestinon® , the subject of application NDA #9829, held by ICN. Barr Laboratories will market the drug product in HDPE bottles of 100's and —

Drug Substances: Pyridostigmine Bromide USP is a white crystalline powder derived from pyridine with the following chemical name/formula/MW: 3-[[(dimethylamino)carbonyl]oxy]-1-methyl-,bromide, C_9H_{13} Br N_2O_2, 261.12. The firm uses the USP tests and specifications to monitor the quality of the drug substance along with in-house tests and specifications for residual solvents and chromatographic purity. The key physicochemical properties monitored for the drug substance that influence batch-to-batch reproducibility are loss on drying and residual solvents.

Formulation and Manufacturing Process: The product formulation, in addition to Pyridostigmine Bromide USP contains Anhydrous Lactose NF, Colloidal Silicon Dioxide NF, and Stearic acid, NF. These inactive ingredients are widely used in the pharmaceutical industry and are not expected to affect the safety and effectiveness of the drug product. The product is manufactured by ——— process of the ——— No inks or dyes are used to imprint the tablets.

The size of the production and biobatch are the same: ——— Tablets.

Method Validation: Pyridostigmine Bromide 60 mg, is a USP compendial item. Therefore method validation testing by a FDA laboratory is not required.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to revise and lower the individual and total impurity limits proposed for the drug substance and drug product release and stability criteria.

Barr is requesting withdrawal of the — tablet packaging configuration due to a —The source of this failure needs to be clarified.

In addition to the above chemistry, manufacturing, and control issues, the labeling review is deficient.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/

HFD-645/BArnwine

HFD-617/NPark/

C. CC Block

ANDA 40-512
DIV FILE
Field Copy

Redacted 28

Page(s) of trade secret and /or confidential commercial information

ANDA 40-512

Pyridostigmine Bromide Tablets, USP

Barr Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-512

2. REVIEW #3

3. REVIEW DATE: September 3, 2003.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002
FDA:	
Telecon Record	29-Oct-2002
Acceptable for filing letter	06-Nov-2002
Original Submission	18-Sep-2002
Telephone Amendment	01-Nov-2002
Amendment	04-Apr-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	24-Jul-2003
Telephone Amendment	16-Sep-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Barr Laboratories, Inc.

Address: 2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Chemistry Review Data Sheet

Representative: Nicholas Tantillo

Telephone: (845) 348-8051

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mestinon
b) Non-Proprietary Name (USAN): Pyridogstimine Bromide Tablets, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Barr Laboratories, Inc. (Barr) proposed ANDA for Pyridostigmine Bromide Tablets USP, 60 mg, is the approved, reference listed drug (RLD) Mestinon® 60 mg, the subject of application NDA #9829, held by ICN Pharmaceutical. The RLD Mestinon ® 60 mg is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations," updated as of 11/20/2001 (Electronic Orange Book).

In accordance with Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act, Barr certifies that in their opinion and to the best of their knowledge, the patents which claim for Pyridostigmine Bromide (the drug product or the drug substance that is a component of the drug product) on which investigations, relied upon for this application, were conducted or that claim an approved use of such drug, have all since expired. To the best of Barr's knowledge, Mestinon ® 60 mg is not listed as having any marketing exclusivity under section 505 (j) (4) D) of the Federal Food, Drug, and Cosmetic Act, and is therefore not entitled to a period of marketing exclusivity.

10. PHARMACOL. CATEGORY: Cholinesterase inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pyridostigmine Bromide

3-[[(Dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide. $C_9H_{13}BrN_2O_2$. 261.12. [101-26-8].

17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	2/12/03	Reviewed by R.Rajagopalan
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/11/02	
Methods Validation	N/A		
Labeling	Acceptable	6/13/03	Koung Lee
Bioequivalence	Acceptable	2/5/03	Moheb Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 40-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Pyridostigmine Bromide 60 mg, is a non-sterile, USP drug. The active agent in this immediate release dosage form is Pyridostigmine Bromide, an orally active cholinesterase inhibitor (inhibits the destruction of acetylcholine by cholinesterase allowing freer transmission of nerve impulses across the neuromuscular junction.). The approved, reference listed drug is Mestinon® , the subject of application NDA #9829, held by ICN. Barr Laboratories will market the drug product in HDPE bottles of 100's.

Drug Substance: Pyridostigmine Bromide USP is a white crystalline powder derived from pyridine with the following chemical name/formula/MW: 3-[[(dimethylamino)carbonyl]oxy]-1-methyl-,bromide, C_9H_{13} Br N_2O_2, 261.12. The firm uses the USP tests and specifications to monitor the quality of the drug substance along with in-house tests and specifications for residual solvents and chromatographic purity. The key physicochemical properties monitored for the drug substance that influence batch-to-batch reproducibility are loss on drying and residual solvents. The API is hygroscopic with a melting point of 152° to 154°; it is freely soluble in water and alcohol and practically insoluble in ether, acetone and benzene.

Formulation and Manufacturing Process: The product formulation, in addition to Pyridostigmine Bromide USP contains Anhydrous Lactose NF, Colloidal Silicon Dioxide NF, and Stearic acid, NF. These inactive ingredients are widely used in the pharmaceutical industry and are not expected to affect the safety and effectiveness of the drug product. The product is manufactured by [redacted] process of the [redacted]. No inks or dyes are used to imprint the tablets.

The size of the production and biobatch are the same: [redacted], Tablets.

Method Validation: Pyridostigmine Bromide 60 mg, is a USP compendial item. Therefore method validation testing by a FDA laboratory is not required.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm reduced the specifications for the level of impurities in the active ingredient to be in agreement with the specifications provided by the [redacted]. The related substances release and stability criteria was also reduced for the drug product. [redacted] percent of the exhibit batch was packaged in the 100's container closure; the firm ceased to seek approval for the product packaged in the [redacted] configuration as originally proposed. This configuration failed [redacted]. It met stability criteria for the product stored under room temperature conditions during the twelve months testing intervals.

The product packaged in the 100's container/closure configuration met the stability and release criteria. Proposed specifications that assess product quality are acceptable. CMC issues were addressed. Labeling and Bio reviews are acceptable. The application can be approved as amended.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/9/3/03

HFD-645/BArnwine/9/26/03

HFD-617/NPark/9/17/03

C. CC Block

ANDA 40-512
DIV FILE
Field Copy

Redacted 25

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

BIOEQUIVALENCE REVIEW(S)

1.1
Sayed

JAN 31 2003

Pyridostigmine Bromide Tablets USP
60 mg
ANDA #40-512
Reviewer: Moheb H. Makary
40512N0902.doc

Barr Laboratories,
Pomona, NY
Submission Date:
September 18, 2002

REVIEW OF A BIOEQUIVALENCE STUDY AND DISSOLUTION TESTING

The firm submitted a single dose fasting bioequivalence study and dissolution data on its 60 mg pyridostigmine bromide tablet.

Background

Mestinon^{R} (pyridostigmine bromide) is an orally active cholinesterase inhibitor. It is useful in the treatment of myasthenia gravis. It inhibits the destruction of acetylcholine by cholinesterase and thereby facilitates transmission of nerve impulses across the neuromuscular junction.

The size and frequency of the dosage must be adjusted to the needs of the individual patient. The average dose is ten 60-mg tablets daily, spaced to provide maximum relief when maximum strength is needed. In severe cases as many as twenty-five tablets a day may be required, while in mild cases one to six tablets a day may suffice.

Pyridostigmine is a synthetic quaternary ammonium compound that is pharmacologically similar to neostigmine and ambenonium.

Pyridostigmine bromide is poorly absorbed from the GI tract. It undergoes hydrolysis by cholinesterases. It is also metabolized by microsomal enzymes in the liver. Approximately 80-90% of a dose of pyridostigmine is excreted unchanged by the kidneys. Although patients with myasthenia gravis may show considerable individual variation in urinary excretion patterns, pyridostigmine and 7 metabolites, including the major metabolite 3-hydroxy-N-methylpyridinium, have been detected in urine up to 72 hours after a single IV dose.

Bioequivalence Requirements:

The Division of Bioequivalence requested the following information in responses to Control Documents 00-095 (Barr, 03/09/00); 00-454 (Wiesen, 10/25/00); 00-518 (Barr, 12/01/00); 01-166 (Corepharma LLC, 03/15/01); 01-284 (Wiesen, 05/24/01); and 01-413 (Impax, 08/12/01):

(a) A single dose, two-treatment, two-period, fasting bioequivalence study comparing the test product, pyridostigmine bromide tablets, 60 mg, with the reference listed drug product, Mestinon^{R} tablets, 60 mg.
(b) Measurement of the parent compound, pyridostigmine, in plasma.
(c) Comparative dissolution testing.

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]

Clinical Study Dates: 06/23/02 to 06/30/02

Analytical Facility [redacted]

Analytical Study Dates: 07/02/02 to 07/09/02

TREATMENT INFORMATION

Treatment ID:	Test	Reference
Test or Reference:	T	R
Product Name:	Pyridostigmine Bromide Tablets USP	Mestinon^{R} Tablets
Manufacturer:	BARR LABORATORIES	ICN PHARMACEUTICALS, INC.
Manufacturing Date:	05/09/02	NA
Expiration Date:	---	07/03
ANDA Batch Size:	[redacted]	NA
Strength:	60 mg	60 mg
Dosage Form:	Tablet	Tablet
Batch/Lot #	401332001R	1G0095
Assayed Potency	101.9%	101.0%
Content Uniformity CV%)	101.3% (1.6%)	102.4% (1.9%)
Dose Administered:	60 mg	60 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

Randomized:	Y	Design Type:	Two-way Crossover
No. of Sequences:	2		
No. of Treatments:	2	Washout Period:	7 Days
No. of Periods:	2		

DOSING:

Single or Multiple Dose:	Single
Volume of Water Intake:	240 mL
Route of Administration:	Oral

SUBJECTS:

Research Ethics Board Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	36
No. of Subjects Completing:	33
No. of Subjects Plasma Analyzed:	33
Gender Included:	15 Males and 21 Females
Healthy Volunteers Only:	Y
Age, Years:	22-47 (mean:23.2)
RACE	
Hispanic	5.6%
Black	2.8%
Caucasian	91.6%
No. Dropouts	3

Subject #30 elected to withdraw prior to the period I 10-hour sampling collection.
Subject #32 elected to withdraw prior to the period I 6-hour sampling collection.
Subject #19 elected to withdraw prior to period II dosing.

BLOOD SAMPLING: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours.

Analytical method

Redacted _____

Page(s) of trade secret and /or confidential commercial information

Comments on the Analytical Method: The analytical method and data are acceptable.

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for pyridostigmine. The reviewer verified the accuracy of AUC data, and performed the analysis of variance on each pharmacokinetic parameter using SAS GLM procedure. An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

In Vivo Results:

Subjects were monitored for adverse events throughout the study as specified in the protocol. No serious adverse events occurred during the study. A summary of adverse events is reported on page 06-203 (Vol.1.2). A total of twenty-three adverse events were reported: 13 following administration of the test product, 10 following administration of the reference product.

The plasma concentrations and pharmacokinetic parameters for pyridostigmine are summarized in Table I.

TABLE I

ARITHMETIC MEAN PYRIDOSTIGMINE PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME (CV%) IN 33 SUBJECTS -- FASTING BE STUDY (R00-700)

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00 .	0.02 (394)	.
0.5	8.95 (69)	9.89 (77)	0.91
1	21.60 (41)	25.85 (46)	0.84
1.5	32.77 (55)	33.00 (39)	0.99
2	32.39 (43)	34.74 (44)	0.93
2.5	30.04 (39)	29.18 (43)	1.03
3	27.44 (39)	25.83 (39)	1.06
3.5	24.30 (39)	23.09 (38)	1.05
4	21.75 (37)	20.89 (39)	1.04
5	16.76 (39)	16.57 (41)	1.01
6	12.72 (45)	12.22 (39)	1.04
7	9.91 (41)	9.59 (43)	1.03
8	7.55 (44)	7.49 (47)	1.01
10	5.28 (47)	5.09 (44)	1.04
12	3.84 (68)	3.53 (49)	1.09
16	1.73 (46)	1.73 (50)	1.00
24	1.03 (76)	0.89 (65)	1.16

PARAMETRIC DATA: MEAN (%CV) IN 33 SUBJECTS

PK Parameter	N	Test Treatment A	N	Reference Treatment B	*Ratio(A / B)
AUC(0-t) [ng-hr/mL]	33	192.1 (35%)	33	190.7 (35%)	1.00
AUCinf [ng-hr/mL]	32	195.5 (35%)	32	194.8 (36%)	1.00
Cmax [ng/mL]	32	38.3 (44%)	33	38.6 (38%)	0.98
Tmax [hr]	33	1.97	33	1.87	
K_{el} [1/hr]	32	0.157	32	0.155	
$T_{½}$ [hr]	32	4.70	38	4.83	

*Ratios are based on geometric means

PK PARAMETER	RMSE	90% C.I.
Ln AUC(0-t) [ng.hr/mL]	0.222	91.3 to 109.9
Ln AUCinf [ng.hr/mL]	0.219	90.9 to 109.4
Ln Cmax [ng/mL]	0.260	87.7 to 109.0

The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax for pyridostigmine. The reviewer's calculations are similar to those submitted by the firm.

Formulation: (Vol. C1.1, p #06-2)

Ingredient	Test Product (mg/Tablet)
Pyridostigmine Bromide	60.0
Lactose	[redacted]
Silicon Dioxide, Colloidal	[redacted]
Stearic Acid	[redacted]
Total Weight:	375.0

* [redacted]

Dissolution Testing: (USP method)

Method: USP 25 apparatus 2 (paddle) at 50 rpm
Medium: 900 mL of water
Number of Tablets: 12
Specification: NLT 80% (Q) of the labeled amount of pyridostigmine bromide is dissolved in 60 minutes
Dissolution results are shown in Table II.

Table II

	TEST PRODUCT, 60 mg Lot No.: 401332001R				REFERENCE PRODUCT, 60 mg LOT NO.: 1G0095			
Time, minutes	Mean	Min	Max	CV%	Mean	Min	Max	CV%
10	27	[redacted]		8.4	30	[redacted]		8.4
20	48			6.3	58			6.3
30	74			4.0	88			4.0
45	99			2.0	100			2.0
60	100			1.2	101			1.2
90	100			1.2	100			1.2

Comments:

1. The firm's *in vivo* bioequivalence study conducted on its pyridostigmine bromide tablet, 60 mg, under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions for pyridostigmine.

2. The dissolution testing conducted by the firm on its pyridostigmine bromide tablets, 60 mg, lot No. 401332001R, is acceptable.

3. All inactive ingredients were reviewed and found to be present in the formulation at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

Recommendations:

1. The single-dose fasting bioequivalence study conducted by Barr Laboratories on its pyridostigmine bromide tablet, USP, 60 mg, lot #401332001R, comparing it with ICN Pharmaceuticals' Mestinon^{R} tablet, 60 mg, has been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Barr Laboratories on its pyridostigmine bromide tablets, USP, 60 mg, lot #401332001R, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 25 Apparatus 2 (Paddle) at 50 rpm.

The test product should meet the following specifications:

> Not less than 80% (Q) of the labeled amount of pyridostigmine bromide is dissolved in 60 minutes.

From bioequivalence viewpoint, the firm has submitted acceptable information regarding *in vivo* bioequivalence and *in vitro* dissolution testing.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED
FT INITIALLED GJP SINGH Date 1-15-03

Concur: for Date: 1/31/03
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 1-10-03, 1-14-03, 40512N0902.doc
cc: ANDA #40-512, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-512 APPLICANT: BARR LABORATORIES

DRUG PRODUCT: PYRIDOSTIGMINE BROMIDE TABLETS USP, 60 MG

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

We acknowledge that the dissolution testing will be incorporated into your stability and quality control programs as specified in the USP 25.

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

Sincerely yours,

Barbara Myers Lowe

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

CC: ANDA #40-512
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

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Printed in final on 1/14/03

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader G. Singh GSPS 1-15-03
for HFD-650/ D. Conner BW 1/31/03

BIOEQUIVALENCY - ACCEPTABLE submission date: 9-18-02

1. **FASTING STUDY** (STF) Strengths: 60 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:40-512	SPONSOR: BARR LABORATORIES
DRUG AND DOSAGE FORM:	Pyridostigmine Bromide Tablets USP
STRENGTH:	60 mg
TYPE OF STUDY:	Single-Dose, Fasting
CLINICAL STUDY SITE:	
ANALYTICAL SITE:	

STUDY SUMMARY: Acceptable.
DISSOLUTION TESTING: Acceptable.

DSI INSPECTION STATUS

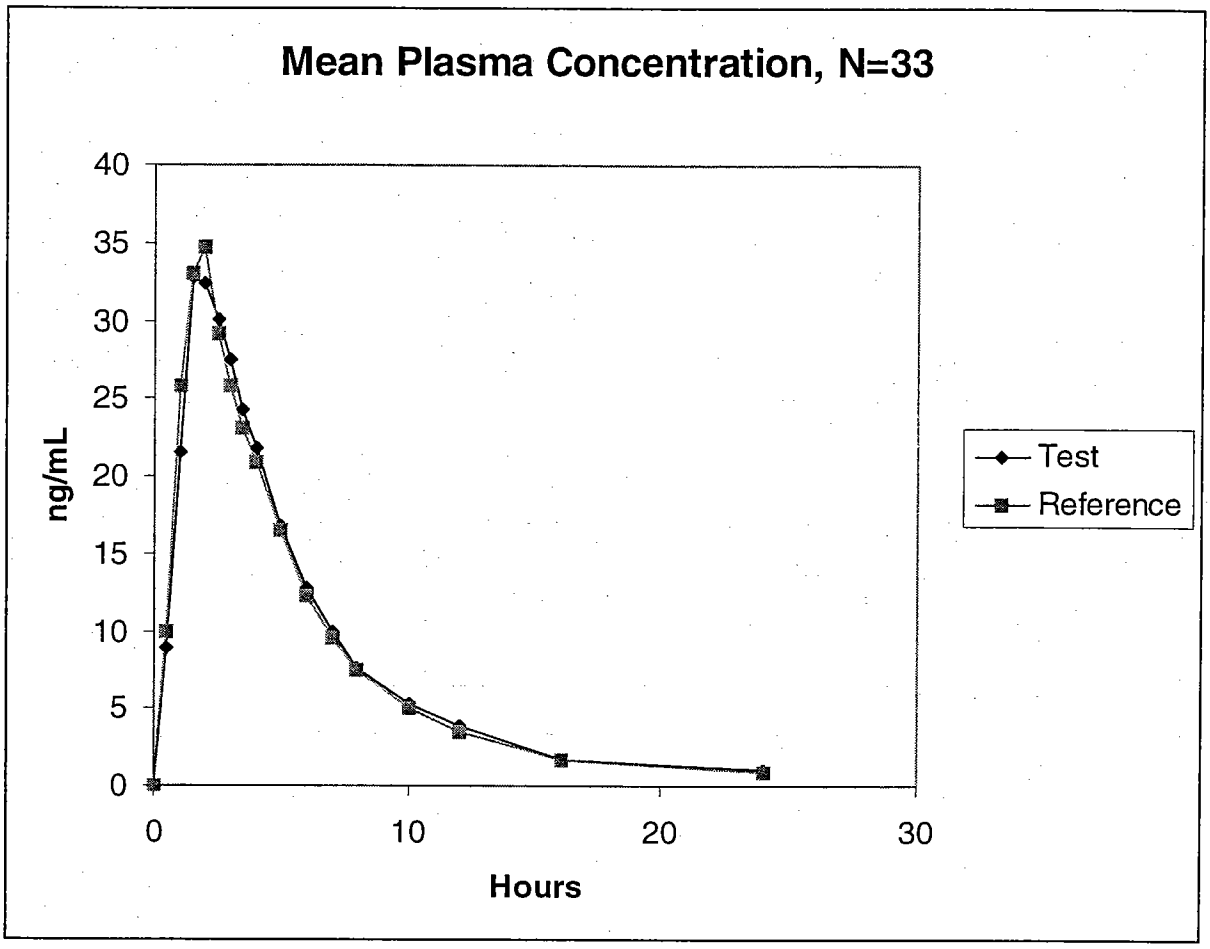
Inspection needed: No.	Inspection status:	Inspection results:
First Generic No. New facility _____ For cause _____ Other _____		

PRIMARY REVIEWER: Moheb H. Makary, Ph.D. BRANCH: 3
INITIAL: MHM DATE: 1/14/03

TEAM LEADER: GJP SINGH, Ph.D. BRANCH: 3
INITIAL: Gurpal Singh DATE: 1-15-03

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: BPC DATE: 1/31/03



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ON ORIGINAL

Fasting Study, ~~~ R00-700

1	2	2	12	20.3	107.96	0.1822	3.81	110.49
1	2	1	22	44.8	177.13	0.1916	3.62	180.11
2	2	2	11.5	60.7	191.38	0.103	6.73	198.05
2	2	1	21	45.2	189.69	0.189	3.67	193.27
3	1	1	12	24	143.08	0.1432	4.84	148.49
3	1	2	22	14.6	82.48	0.068	10.2	92.87
4	1	1	11.5	44.9	226.49	0.1475	4.7	233.34
4	1	2	22	36.7	199.5	0.1708	4.06	204.45
5	2	2	11.5	16.4	94.5	0.1402	4.94	97.78
5	2	1	22	21.4	126.11	0.1648	4.21	128.89
6	2	2	11.5	47.4	239.75	0.1567	4.42	247.72
6	2	1	21.5	29.9	161.6	0.1698	4.08	165.65
7	1	1	12	52.1	273.19	0.1729	4.01	280.13
7	1	2	21	25.1	136.36	0.1737	3.99	139.34
8	2	2	11.5	32.1	142.12	0.1613	4.3	147.17
8	2	1	21.5	25.1	137.87	0.1129	6.14	147.79
9	2	2	12	18.5	142.29	0.1206	5.75	154.64
9	2	1	22.03	32.4	199.09	0.1439	4.82	207.99
10	1	1	11.5	27	129.48	0.1591	4.36	134.33
10	1	2	21.5	32.3	179.66	0.1571	4.41	184.8
11	2	2	11.5	38.7	150.02	0.2012	3.45	152.33
11	2	1	21.5	26.7	113.56	0.1705	4.07	117.17
12	1	1	13.5	47.3	303.68	0.1657	4.18	314.3
12	1	2	22	76.2	301.72	0.1835	3.78	308.91
13	1	1	12.5	36.7	272.91	0.1394	4.97	280.59
13	1	2	22.5	43.8	277.88	0.1325	5.23	286.56
14	1	1	11	12.5	78.92	0.2406	2.88	81.21
14	1	2	21.5	14.1	103	0.1913	3.62	104.7
15	1	1	12	36.1	215.51	0.1729	4.01	221.87
15	1	2	22	23.4	112.2	0.2696	2.57	114.24
16	1	1	13	51	195.2	0.1358	5.1	202.94
16	1	2	22	61.9	231.58	0.1159	5.98	238.42
17	2	2	12	44.7	208.83	0.1695	4.09	211.8
17	2	1	22	45.4	175.38	0.1987	3.49	178.02
18	1	1	12	23.4	113.3	0.1749	3.96	114.98
18	1	2	23	28	133.31	0.1249	5.55	136.83
20	2	2	12	25	142.54	0.1247	5.56	149.97
20	2	1	22	22.9	116.15	0.1457	4.76	122.44
21	1	1	12	44.2	202.35	0.2216	3.13	203.65
21	1	2	21.5	41	174.53	0.2094	3.31	176.27
22	2	2	11.5	92.9	294.35	.	.	.
22	2	1	21.5	57.5	254.5	.	.	.
23	1	1	12.5	30.1	192.75	0.1615	4.29	196.29
23	1	2	23.5	40.5	259.61	0.1933	3.59	262.59
24	1	1	12	41.4	226.5	0.1696	4.09	232.92
24	1	2	22	41.4	219.68	0.119	5.82	229.68
25	1	1	11.5	60.3	236.53	0.0915	7.57	248.44
25	1	2	21.5	48.4	217.73	0.0899	7.71	230.73
26	2	2	13	30	151.44	0.1273	5.45	160.16
26	2	1	23	24.5	123.71	0.1123	6.17	128.76
27	2	2	12.5	35.9	248.01	0.151	4.59	258.74
27	2	1	22	33.5	210.8	0.1455	4.76	220.43
28	2	2	12.5	32.4	169.22	0.0685	10.13	186.46
28	2	1	22	55.4	242.08	0.1191	5.82	249.87
29	2	2	11.5	44.4	301.32	0.1431	4.84	311.73
29	2	1	21.5	42.6	250.41	0.1436	4.83	260.15

31	2	2	11.5	25.8	105.57	0.1838	3.77	108.08
31	2	1	21	41.3	149.53	0.1801	3.85	153.34
33	1	1	12.05	69	289.16	0.1652	4.2	299.09
33	1	2	21.5	66.3	304.62	0.1148	6.04	312
34	2	2	13	43	241.93	0.186	3.73	246.09
34	2	1	21.5	46.9	259.58	0.1359	5.1	266.03
35	2	2	11	18.4	75.91	0.1891	3.67	77.4
35	2	1	21	32.9	122.96	0.1925	3.6	125.25
36	1	1	12	37.4	234.42	0.1458	4.76	245.81
36	1	2	23	51	349.86	0.1235	5.61	364.6

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-512

NOV 6 2002

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
Pomona, NY 10970

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.

Reference is made to the telephone conversation dated October 29, 2002 and to your correspondence dated November 1, 2002.

NAME OF DRUG: Pyridostigmine Bromide Tablets USP, 60 mg

DATE OF APPLICATION: September 18, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 19, 2002

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:

Nicole Park
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

Please file in ANDA 40-572 21 ARNWINE, D

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:40-512	SPONSOR: BARR LABORATORIES
DRUG AND DOSAGE FORM:	Pyridostigmine Bromide Tablets USP
STRENGTH:	60 mg
TYPE OF STUDY:	Single-Dose, Fasting
CLINICAL STUDY SITE:	
ANALYTICAL SITE:	

STUDY SUMMARY:	Acceptable.
DISSOLUTION TESTING:	Acceptable.

DSI INSPECTION STATUS

Inspection needed: No.	Inspection status:	Inspection results:
First Generic No. New facility ____ For cause ____ Other ____		

PRIMARY REVIEWER: Moheb H. Makary, Ph.D. BRANCH: 3
INITIAL: MHM DATE: 1/14/03

TEAM LEADER: GJP SINGH, Ph.D. BRANCH: 3
INITIAL: Gurpal Singh DATE: 1-15-03

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DPC DATE: 1/31/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-512

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 16, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Telephone Amendment

Reference is made to our submission for an Abbreviated New Drug Application submitted on September 18, 2002, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pyridostigmine Bromide Tablets, USP 60mg.

Reference is also made to a September 4, 2003 phone conversation between Damaris Maldonado of FDA and William Kwok of Barr Laboratories, Inc (Barr). Damaris requested that Barr lower the ——— specification for the drug product release and stability criteria, and stated that this information should be submitted in a Telephone Amendment.

——— specification

As requested by the Agency, Barr has tightened the ——— specification for the drug product release and stability criteria from NMT ——— to NMT ———

Enclosed in Section XIV, please find the following supporting documentation:

- Finished Product Test Method, MTH-133 Version 4.4
- Quality Control Analytical Specifications & Test Record for Pyridostigmine Bromide Tablets, USP 60mg, Barr Code 0133 Rev. 4
- Marketed Product Stability Specifications & Test Record for Pyridostigmine Bromide Tablets, USP 60mg, Barr Code 0133 Rev. 2

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SEP 17 2003
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Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 24, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/am

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

Reference is made to our submission for an Abbreviated New Drug Application submitted on September 18, 2002, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pyridostigmine Bromide Tablets, USP 60mg.

Reference is also made to the Agency's facsimile correspondence to Barr Laboratories, Inc. (Barr) dated June 16, 2003 providing chemistry comments. You indicated that Barr's response will be considered to represent a minor amendment. Our responses to your comments follow:

Comment 1:

Please revise your drug substance specifications for the [redacted], and [redacted] impurities to be in agreement with the specifications established by your [redacted].

Response 1:

After a close review of the drug substance data for the impurities stated above, Barr has amended the test method and corresponding specifications and test records to change the limits for [redacted], and [redacted] from NMT [redacted] to NMT [redacted]. These proposed limits are the same as the limits set by the [redacted].

Enclosed in Section VIII, please find the following supporting documentation:

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JUL 25 2003
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- Raw Material Specifications and Test Record, 01-0406, Rev. 4
- Raw Material Test Method for Pyridostigmine Bromide, USP, MTH-110, Version 5.0

N/A 8/5/03

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

Comment 2:

Based on the stability results reported for the drug product and the information submitted by your DMF holder, we recommend lowering the impurity specification for [redacted] for the drug product release and stability criteria.

Response 2:

As requested by the Agency, Barr has tightened the impurity specification for [redacted] from NMT [redacted] to NMT [redacted]

Enclosed in Section XIV, please find the following supporting documentation:

- Finished Product Test Method, MTH-133
- Quality Control Analytical Specifications & Test Record for Pyridostigmine Bromide Tablets, USP 60mg, Barr Code 0133
- Marketed Product Stability Specifications & Test Record for Pyridostigmine Bromide Tablets, USP 60mg, Barr Code 0133

Comment 3:

Please acknowledge that your dissolution specification for release and stability purposes should read NLT (Q) = 80% is dissolved in 60 minutes.

Response 3:

Barr acknowledges the Agency's comment and has revised the dissolution specification to read NLT (Q) = 80% is dissolved in 60 minutes in all applicable documents.

Comment 4:

The proposed drug product assay specification of [redacted] % of label claim as described in the report forms and on page 48 of the amendment is not acceptable. Please revise this stability specification accordingly to the meet shelf life USP criteria of 95.0 % to 105.0%.

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

Response 4:

Barr inadvertently stated the proposed drug product assay specification as [redacted] of label claim in ARD_RPT-405. We have revised the referenced report to read 95.0 to 105.0% of label claim. Please see Section XVI for the update to the above referenced report.

Comment 5:

Your stability data shows that the moisture content in the finished product packaged in the 100 count tablet size, dropped from an initial result of [redacted]% to levels of approximately [redacted] when stored at room temperature at the nine months test station; whereas the moisture level in the product packaged as bulk increased to [redacted], after three months of room temperature storage. Please explain these differing trends observed and how does the level of moisture affect the quality of the finished product with respect to dissolution, related substances and other product attributes. Please explain if the dissolution failure of the product packaged in the [redacted] tablet size is related to the [redacted] content in the finished product.

Response 5:

The Pyridostigmine Bromide Tablets, USP 60mg were stored in bulk without desiccants (see ARD_RPT-415, page 16-68 of the Original Application), and absorbed moisture over time whereas the 100 count tablets showed a decrease in moisture since the tablets were stored with a desiccant and [redacted] seal. Following ARD_PRT-280, Bulk Stability Protocol (see pages 16-22 to 16-28 of the original application), 4 x Desiccant Bags [redacted], were added to the bulk tablets and the bulk stability program was re-initiated at the one month test station. As expected, the bulk tablets with desiccants did not gain moisture and, in fact, mimicked the results of the 100 count tablet size which lost moisture over time when stored under room temperature conditions (see Tables 1 through 4 on the following page).

Redacted 2

Page(s) of trade secret and /or confidential commercial information

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

Comment 6:

Please provide updated long term and intermediate storage stability results.

Response 6:

At this time, Barr is providing up to 12 months of data for product packaged in bottles of 100 tablets stored at intermediate conditions and at room temperature conditions. Enclosed in Section XVI, please find the following supporting documentation:

- ARD_RPT-405, Pyridostigmine Bromide Tablets, USP 60mg (100s count)

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

We acknowledge withdrawal of the portion of the application related to the product packaged in the — tablets size. Please provide information or results of any investigation conducted to determine the cause of [redacted] or the stability studies of the finished product packaged in this configuration.

Response B:

Barr conducted a statistical analysis comparing the 100 to the — tablet size under both room temperature and accelerated stability conditions. The results showed no difference between the two package sizes under room temperature conditions, with only a slight decrease in the average dissolution results. However, under accelerated conditions, there was a sharper decrease in dissolution results for both sizes; with the — tablet size decreasing at a greater rate than the 100 tablet size. At 24 months, the dissolution prediction is — for the 100 tablet size, whereas it is — for the — tablet size. The dissolution limit is NLT (Q) = 80% in 60 minutes. Therefore, the 100 tablet size is predicted to pass dissolution at 24 months but the — tablet size is [redacted] This analysis confirmed the — tablet size [redacted] as the 100 tablet size under accelerated stability conditions. These findings, coupled with Barr's Sales and Marketing Department's re-assessment of the — tablet size as non lucrative, led us to decide not to pursue the — tablet size.

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

An identical copy of this Minor Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Minor Amendment. If you have any questions, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director of Regulatory Affairs

cc. Baltimore District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 21, 2003

Labeling Amendment

ORIG AMENDMENT

N/AF

FPL

Office of Generic Drugs
CDER/ Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ANDA 40-512
Pyridostigmine Bromide Tablets, USP 60 mg

Dear Sir or Madam:

Reference is made to our Approved New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pyridostigmine Bromide Tablets, USP 60 mg.

On May 1, 2003 and May 7, 2003, Barr received labeling comments to comply with the referenced listed drug Mestinon® for the container label and package brochure.

Attached please find 12 final printed container labels and package brochures Revision May 2003, which have been revised according to the above recommendations. Also enclosed is a side-by-side comparison between the Last Submitted and the Proposed container label and package brochure annotating and explaining those sections that are different.

If you have any questions, please contact me by phone at (845) 348-6894 or by fax at (845) 353-3859.

Sincerely,

Salvatore P. Peritore, M.S., R.Ph.
Associate Director, Regulatory Affairs

Enc.

RECEIVED
MAY 22 2003
OGD / CDER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 4, 2003

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Minor Amendment

Reference is made to our submission for an Abbreviated New Drug Application submitted on September 18, 2002, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pyridostigmine Bromide Tablets, USP 60mg.

Reference is also made to the Agency's facsimile correspondence to Barr Laboratories. Inc. (Barr) dated March 11, 2003 providing chemistry comments, and to the November 1, 2002 Telephone Amendment from Barr providing for a bottle of — tablets. In your March 11, 2003 facsimile, you indicated that Barr's response will be considered to represent a minor amendment. Part 1 of Barr's response letter is our request to withdraw the proposed bottle of — tablets. Part 2 contains our response to the chemistry comments.

Part 1

On November 1, 2002 we provided information and data for the addition of a bottle of — tablets. Barr does not intend to package and market Pyridostigmine Bromide tablets in bottles of — tablets, therefore we hereby request that the information and data for the addition of a bottle of — tablets be withdrawn without prejudice to future filing.

Enclosed in Section IV, is an updated abridged side by side labeling comparison of Barr's last submitted package brochure (with 100 counts and — counts) to Barr's newly proposed package brochure (100 counts only). Also enclosed in Section V are 4 copies of the new draft package brochure for the 60mg strength in package size of 100 tablets (4 copies in the archival and review copies, and 1 in the field copy).

Part 2

Comment 1:

— was listed as a process impurity from the drug substance according to the information submitted for your API lot P213208. The revised specifications do not include this impurity. Please include all known impurities/degradation products in the drug substance release and drug product release and stability specifications. Please revise and re-submit.

Response 1:

During the last update of the Raw Material Specifications and Test Record for Pyridostigmine Bromide, USP (01-0406), Barr inadvertently [redacted] as a known specified impurity. However, it was monitored as an individual impurity. Additionally, Barr labeled [redacted], instead of correctly labeling it as [redacted] At this time, Barr is including [redacted] with a proposed limit of NMT [redacted] Additionally, [redacted] is being correctly labeled as [redacted] and will continue to be monitored as a known specified impurity. Please note that our proposed limit of NMT [redacted], for [redacted] conforms with the limit set by the [redacted]

[redacted] has been identified as a process related impurity by the [redacted] Therefore, because it is not a degradation product, Barr will not include [redacted] as a named impurity on the drug product release and stability specifications. This is consistent with the "Guidance for Industry: ANDAs: Impurities in Drug Products" as well as "Q3B Impurities in New Drug Products" which state that process related impurities which are not degradation products do not have to be monitored in the drug product. However, please note that this impurity will continue to be monitored as an unspecified individual impurity in the drug product.
Enclosed in Section VIII, please find the following supporting documentation:

- Raw Material Specifications and Test Record, 01-0406, Rev 3.*
- Raw Material Test Method, MTH-110, Version 3.0.*

* See the history page (the last page) of each document for a complete list of revisions.

Comment 2:

Please provide a list of the manufacturing equipment intended for use in the post-approval batches and compare with the equipment used in the exhibit batch.

Response 2:

The manufacturing master, Master Control No. (MC#) 0133A014 was used to produce the exhibit batch of Pyridostigmine Bromide Tablets, USP 60mg, Lot # 401332001R. The manufacturing master was subsequently updated to MC# 0133A024 for production use. Please note that the equipment intended for use in the post-approval batches is the same as the equipment used in the exhibit batch (see following Table 1).

Table 1

Exhibit Batch	Post-Approval Batches
[redacted]	[redacted]

A comparison of the manufacturing masters (MC# 0133A014 and MC# 0133A024) was provided on pp. 11-13 to 11-14 in Section XI of the original application. For your convenience, the referenced pages are included in Section XI of this submission. Not included

Comment 3:

Please describe the "

Response 3:

As stated in the wavier dated 5/13/02 on pp. 12-6 in Section XII of the original application, the tablets that

Comment 4:

As a result of the , it was recommended to ' requirement from LT to LT . Please provide data to support that this proposed new environmental parameter would not only prevent the drug product to , but also will not affect compliance with the finished drug product release and stability specifications.

Response 4:

After the issue was discovered, the relative humidity ("RH") was changed from LT to LT . This change was recorded on 5/14/02 (the day the acceptable tablets were) for Pyridostigmine Bromide Tablets, USP 60mg, Lot # 401332001R (exhibit batch). This is documented on the humidity chart that was located in the room during of the exhibit batch. A copy of the chart is located in Section XII of this submission. Note that the red line (upper) on the chart represents temperature in degrees Celsius, and the blue line (lower) represents relative humidity in percentage. The remainder of the batch with the RH below 40% was successfully and met both finished product release and stability specifcations for the 100 count package style (please note the count package will no longer be pursued for this product).

Therefore, the data included in the original ANDA submission for exhibit batch #401332001R, which meets the submitted specifications, supports the fact that the proposed new environmental parameter will prevent the drug product from , it did not affect compliance with the finished drug product release and stability specifications for the 100 count package style And all release and stability specifications were met for the 100 count package style.

Comment 5:

The packaging reconciliation records submitted do not include the information for the number of bottles packaged in each one of the four different container configurations. Please provide reconciliation of the amount of tablets issued and the amount of bottles packaged in each one of the different containers.

Response 5:

Packaging reconciliation tables for Job #s 10579, 10580, 10581 and 10582 were provided on pp. 12-34 to 12-35 in Section XII of the original application and included information on the quantity packaged. Table 2 below provides the additional information of the number of bottles packaged in each one of the four different container configurations.

Table 2

Packaging Reconciliation for Pyridostigmine Bromide Tablets, USP 60mg Tablets, Lot #40133200IR			
Package Size	**Packaging Configuration**	**Number of bottles**	**Quantity Packaged (Tablets)**
100 count	**Job # 10579**		
	120cc Thick Walled HDPE bottle		
	For stability purposes	[redacted]	[redacted] tablets
	For bio Study studies	[redacted]	[redacted] tablets
	For packaging purposes	[redacted]	[redacted] tablets
	For waste	--	[redacted] tablets
	Job # 10581		
	120cc non Thick Walled HDPE bottle		
	For stability studies		[redacted] tablets
	For waste	--	[redacted] tablet
[redacted] count	**Job # 10580**		
	[redacted] Thick Walled HDPE bottle		
	For bulk stability studies	--	[redacted] tablets
	For stability studies	[redacted]	[redacted] tablets
	For packaging purposes	[redacted]	[redacted] tablets
	For waste	--	[redacted] tablets
	Job # 10582		
	[redacted] non Thick Walled HDPE bottle		
	For stability studies	[redacted]	[redacted] tablets
	Total:	[redacted]	[redacted] tablet

Comment 6:

Please revise your dissolution criteria in the release and stability specifications according to the USP monograph.

Response 6:

The dissolution criteria included in the original ANDA submission, Section XIV, on pp. 14-4 to 14-27 (see Table 3) is identical to the dissolution criteria specified in the current USP monograph for Pyridostigmine Bromide Tablets. The dissolution criteria is included in Barr's release and stability specifications.

Table 3: Pyridostigmine Bromide Tablets, 60mg Dissolution Specifications and Parameters

MTH-133 Version 3.0	**Specification**
Apparatus: USP Apparatus 2 (paddle)	**Q = 80%; Spl. Time 60 minutes. Meets USP <711> S1, S2, or S3 criteria as appropriate**
Medium: Water	
Volume: 900mL	
Rotation Speed: 50 rpm	
Temperature: 37 +/- 0.5°C	

Comment 7:

Under the ——— stress of the impurities, assay and content uniformity test methods you state in the validation report that an unknown peak eluting at about two minutes was significantly greater. Peak recovery for the Pyridostigmine peak from the impurities evaluation is reported as ——— and ——— from the assay method. Please clarify the statements made about the unknown eluting at two minutes and address peak purity from the ——— results. Please provide also the integration reports.

Response 7:

[redacted]

Comment 8:

Please provide all available room temperature stability data for the product packaged in the different container/closure configurations, including data for all known and unspecified impurities.

Due to the failing results of the accelerated stability studies for the product packaged in the [redacted] count bottles and to the significant decreasing trend in the dissolution results observed for the product packaged in the 100 count bottles under accelerated conditions, the requested expiration data can not be granted from the information available. To support the requested 24 month expiration dating period, please submit 24 months room temperature stability data in both container/closure systems.

Response 8:

We disagree with your comment that, to support the requested 24 month expiration dating, Barr should submit 24 month room temperature data:

1. In Part 1 of this Minor Amendment, we requested that information and data for the bottles of [redacted] tablets be considered withdrawn from the application, since Barr does not intend to package and market pyridostigmine bromide tablets in bottles of [redacted] tablets. Therefore the accelerated stability data on bottles of [redacted] tablets are not relevant to the proposed bottles of 100 tablets.

2. The change in dissolution of pyridostigmine bromide tablets packaged in bottles of 100 observed following storage for 3 months at accelerated conditions is not significant (comment 8, "...the significant decreasing trend...") based on the agency's own definition of a "significant change". FDA guidance documents [1,2] define a "significant change" in dissolution as a failure to meet the acceptance criteria for dissolution for 12 dissolution units. The dissolution acceptance criteria for pyridostigmine bromide tablets are the current USP criteria, i.e., NLT 80% in 60 minutes. After 3 months storage at accelerated conditions, the Barr product meets the acceptance criteria.

3. Both guidance documents recommend that when a significant change occurs, intermediate or long term data through the proposed expiration date will be necessary. For an ANDA, the tentative expiration dating would be determined based on the available data from the additional study. This is the approach OGD is taking with respect to this ANDA. But with the Barr product, a significant change has not occurred. In fact, following accelerated storage, the Barr product fully complies with

the proposed specifications. Under these circumstances, FDA cannot put aside acceptable 3-month accelerated stability data and instead require the submission of 24 months room temperature data to support a 24-month expiration dating period.

4. In this amendment, we are providing up to 9 months of data for product packaged in bottles of 100 tablets stored at intermediate conditions and at room temperature conditions. The Barr product fully complies with the proposed specifications. Enclosed in Section XVI is an updated stability report for Pyridostigmine Bromide Tablets, USP 60mg (ARD_RPT-405 Version 2.0).

Table 4: 100's in 120cc thick walled HDPE bottle

Interval	Initial	1M	2M	3M	6M	9M
Specification	**Q =80% at 60mins**					
	% Dissolved (Mean)					
Accelerated (40°C/75% RH)	100	90	92*	89	N/A	N/A
Intermediate (30°C/60% RH)	100	99	100	101	96	96
Room Temperature (25°C/60% RH)	100	N/A	N/A	101	97	98

*** Average of 12 dosage units.**

Table 5: 100's in 120cc non thick walled HDPE bottle

Interval	Initial	1M	2M	3M	6M	9M
Specification	**Q =80% at 60mins**					
	% Dissolved (Mean)					
Accelerated (40°C/75% RH)	100	99	93	87*	N/A	N/A
Intermediate (30°C/60% RH)	100	98	101	97	96	92
Room Temperature (25°C/60% RH)	100	N/A	N/A	101	99	98

*** Average of 12 dosage units.**

Based on the above information we continue to believe that a tentative 24-month expiration date is appropriate.

[1] Guidance for Industry, Q1A Stability Testing of New Drug Substance and Products, August 2001, Revision
[2] Guidance for Industry, Stability Testing of Drug Substances and Drug Product, Draft Guidance, June,1998.

An identical copy of this Minor Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Minor Amendment. If you have any questions, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Miriam Knox for

Nicholas C. Tantillo
Senior Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

cc. Baltimore District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 1, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Paras Patel

NEW CORRESP
NC
-PMP
(Telecon-Request-Info)
11/5/02

REFERENCE: **ANDA # 40-512**
Pyridostigmine Bromide Tablets, USP 60mg
Telephone Amendment

Reference is made to our submission for an Abbreviated New Drug Application submitted on September 18, 2002, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pyridostigmine Bromide Tablets, USP 60mg.

Reference is also made to an October 29, 2002 phone conversation between Paras Patel of FDA and Nicholas C. Tantillo of Barr Laboratories, Inc (Barr) and to a subsequent phone conversation on the same date between Mr. Patel and Linda O'Dea, and Elisabeth Noble Gray of Barr. Mr. Patel explained that a minimum of — units needed to be packaged in the containers proposed for marketing for the application to be accepted for filing. Although Barr had packaged over — units in bottles of 100 and — counts, the application includes a statement indicating the Barr has decided to seek approval for only the 100 count package size. Therefore, less than — units were packaged in the containers proposed for marketing and the application can not be accepted for filing as submitted.

At this time, Barr has decided to seek approval for the 100 and — count package sizes and is submitting all information pertaining to the — count package including labeling, container/closure information, and stability data. Mr. Patel stated that this information should be submitted to his attention in a Telephone Amendment to ANDA 40-512.

In support of this Telephone Amendment, the following documentation is provided:

Section IV. Comparison between Generic Drug and Reference Listed Drug to support marketing in the — count

- Side by Side comparisons of Barr's proposed container label with reference listed drug

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Section V. Labeling to support marketing in the — count

- Container Label: 4 copies of draft blister card for the package size of —Tablets (4 copies in the archival and review copies, and 1 copy each in the field copies)
- Package Brochure: 4 copies of the draft brochure (4 copies in the archival and review copies, and 1 copy each in the field copies)

Section XI. Manufacturing and Processing Instructions to support marketing in the— count

- Blank Batch Records: Packaging Masters

Section XIII. Packaging Materials Controls to support marketing in the — count

- Summary of Packaging System
- Components Specifications and Test Data

Section XVI. Stability of Finished Dosage Form to support marketing in the —, count

- Stability Data

An identical copy of this Telephone Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Telephone Amendment. If you have any questions, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director of Regulatory Affairs

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cc. Baltimore District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 18, 2002

505(j)(2)(A) OK
06-Nov-2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **Abbreviated New Drug Application**
Pyridostigmine Bromide Tablets, USP 60mg

In accordance with the regulations promulgated under 505 (j) of the Food, Drug and Cosmetic Act, and as amended, Barr Laboratories, Inc. is submitting this Abbreviated New Drug Application for Pyridostigmine Bromide Tablets, USP 60mg.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of **5 volumes.** The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of **2 volumes**. The bioequivalence part of the review copy is contained in orange binders and consists of **4 volumes.** Since Barr validated a non USP finished product test method for Assay, Content Uniformity, and Impurities/Degradation Products, two additional copies of the method validation package are included with this application (one for the archival copy and one for the review copy). Barr commits to resolve any issues identified in the enclosed method validation procedures after approval.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, is a Debarment Certification Statement. A Field Copy of this application has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided in this application.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

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REFERENCE: **Abbreviated New Drug Application**
Pyridostigmine Bromide Tablets, USP 60mg

If you have any questions concerning this application, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director of Regulatory Affairs

cc. Baltimore District Office