

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-771

CHEMISTRY REVIEW(S)

Addendum # 2 to Chemist's Review # 3:

ANDA 74-771 (Cholestyramine for Oral Suspension USP Powder)

Amendments submitted after completion of Addendum to CR # 3
(Closed):

Telephone Amendment: 7-1-97

1. Chemistry Issues were previously closed per Review # 3 for this ANDA.
2. FPL - acceptable per review completed by C. Holquist on 6-5-97 after review of amendments dated 5-14-97 and 5-29-97 per addendum to CR # 3.
3. Based on update of specifications for the drug substance and drug product cited in USP 23, Supplement # 6, Dr. Allen Rudman during his pre-approval QA review recommended that update should be done. Baker Norton was called to request telephone amendment which should include a copy of revised specifications for drug substance to include OVI testing specification and release specifications for the drug product to include the Exchange Capacity and delete assay test per USP 23, Supplement # 6.

In response, Baker Norton Pharmaceutical (BNP) submitted telephone amendment on 7-1-97. In this amendment, BNP submitted revised drug substance Cholestyramine specifications and included OVI per Supplement # 3 and # 6 to USP 23. BNP also submitted a clarification from the drug substance supplier, _____ Company that only _____ of the listed chemicals in the OVI test (USP <467>) is only expected to be present in Cholestyramine based on their manufacturing process. The limit proposed by BNP is 500 ppm per current USP requirements. It is acceptable per ICH Q3C (Draft) document which recommends a limit of 600 ppm. Maximum dosage is 8 g/day of Cholestyramine and the dosage form contains _____ of the active. _____ also confirmed in this submission that test results of their Cholestyramine resin are less than _____ ppm.

In this telephone amendment, BNP also confirmed that they will continue to use validated in-house assay method (STP _____) for their drug product submitted in their ANDA. Although, the USP has changed their method from the previously named assay to that currently named Exchange Capacity, BNP will continue to use the validated method

4. EER Status - pending.

*EER acceptable on 6/27/97
/S/*

Addendum to Chemist's Review # 3:

ANDA 74-771 (Cholestyramine for Oral Suspension USP Powder)

Amendments submitted after completion of CR # 3 (Closed):

Amendment (FPL): 5-14-97

Amendment (FPL): 5-29-97

1. Chemistry Issues were previously closed per Review # 3 for this ANDA.
2. FPL - acceptable per review completed by C. Holquist on 6-5-97 after review amendments dated 5-14-97 and 5-29-97.
3. Bio status became acceptable per letter dated 5-29-97 issued to firm by the Division of Bioequivalence after review of 11-27-96 amendment.
4. EER Status - pending.
5. No change in DMF status is noted since completion of CR # 3.

Conclusion: ANDA remains approvable pending acceptable EER.

Endorsements:

6/23/97

Attachment 1

Cholestyramine

Active Drug Substance Specification

Page(s) /

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releasable.

Active Specification

Attachment 2

Vendor Certification

Page(s)

1

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releasable.

Vendor Cert.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

ANDA 74-771 Cholestyramine for Oral Suspension, USP Powder, 4 gram

April 3, 1997

Douglas Sporn, Director
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, MD 20855-2773

By Facsimile: 301-827-4337

NEW CORRESP

FACSIMILE AMENDMENT

Reference: ANDA 74-771 Cholestyramine for Oral Suspension, USP Powder, 4 gram
(Anhydrous Cholestyramine resin per packet and scoopful)

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, herewith please find an amendment to Baker Norton Pharmaceuticals, Inc. (BNP) Abbreviated New Drug Application, ANDA 74-771, for Cholestyramine for Oral Suspension, USP dated October 20, 1995. Reference is also made to your facsimile "Chemistry Comments to be Provided to the Applicant and Labeling Deficiencies", sent March 4, 1997. A copy of this facsimile has been included for your reference.

BNP is amending the application by responding to the numbered deficiencies and providing the supportive documentation as corresponding numbered exhibits.

RECEIVED

APR 07 1997

GENERIC DRUGS

000001

Page(s) 2

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Chemistry Comments
4/3/97 #38

Labeling Deficiencies:

The container labels and insert labeling have been revised as instructed by the Labeling Review Branch. Included in Exhibit 5 are:

Twelve (12) representative printed copies of the single dose packet container labeling;

Twelve (12) representative printed copies of the can container labeling;

Four (4) draft copies of the package insert.

It is noted that FDA reserves the right to request further changes in our labels and/or labeling. To facilitate review of this submission and in accordance with 21 CFR 314.94(a)(8)(iv), BNP has provided a side-by-side comparison of our proposed labeling in Exhibit 6.

Exhibit 7 contains a copy of the referenced March 4, 1997 facsimile from the Food and Drug Administration to BNP for your convenience..

I trust the information provided in this amendment will sufficiently answer your questions, but if additional information is required, please call me at (305) 575-6336.

Sincerely,



Steven M. Viti, Ph.D.

Associate Director, Regulatory Affairs

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Chemistry Closed

1. CHEMISTRY REVIEW NO. 3

2. ANDA # - 74-771

3. NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceutical Inc. (BNP)
8800 N.W. 36th Street
Miami, FL 33178-2402

4. BASIS OF SUBMISSION

Adequate per CR # 1.

The listed drug products are Questran (eq 4 gm resin/packet) by Bristol Myers Pharmaceutical Laboratories approved in NDA # 16-640 001 (packet).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Cholestyramine For Oral Suspension, USP Powder

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 10-20-95

Amendment: 6-13-96

Major Amendment: 10-18-96 (Response to NA letter 4-18-96)

NC (BIO): 11-27-96 (Response to bio letter dated 5-20-96)

* Facsimile Amendment: 4-3-97

FDA:

Accepted for filing Letter Date: 12-8-95

NA Letter (chemistry + Labeling): 4-18-96

Deficiency letter (BIO): 5-20-96

NA letter via Fax: 3-4-97

10. PHARMACOLOGICAL CATEGORY

1. Reduction of elevated serum cholesterol.

2. Relief of pruritus associated with partial biliary obstruction.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

for

13. DOSAGE FORM
Powder (Oral)

14. POTENCY
4 g/Dose

15. CHEMICAL NAME AND STRUCTURE
NAME: Cholestyramine is a synthetic anion ion-exchange polymer in which quaternary ammonium groups are attached to a copolymer of styrene and divinylbenzene.

STRUCTURE: See CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS

1. Referenced DMF for is adequate per M. Shaikh's review dated 6-5-96. No new information is submitted since last review.
2. Adequate information is submitted regarding manufacturing, testing, container/closure systems and packaging facilities of the drug product.
3. Release and stability specification for the drug product became acceptable.
4. Adequate data is submitted to support 24 months of expiration dating period for the drug product.
5. A revised EER has been submitted with new address of the packaging facility (PCI of Virginia) on 2-27-97.
6. FPL has been requested to the firm via FAX dated 3-4-97.
7. Bio review of firm response dated 11-27-96 is pending review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable FPL, Bio status and EER.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 4-8-97
Revised on 4-15-97

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Chemistry Review #3

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

ANDA 74-771 Cholestyramine for Oral Suspension, USP Powder, 4 gram

April 3, 1997

Douglas Sporn, Director
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, MD 20855-2773

By Facsimile: 301-827-4337

NEW CORRESP

FACSIMILE AMENDMENT

Reference: ANDA 74-771 Cholestyramine for Oral Suspension, USP Powder, 4 gram
(Anhydrous Cholestyramine resin per packet and scoopful)

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, herewith please find an amendment to Baker Norton Pharmaceuticals, Inc. (BNP) Abbreviated New Drug Application, ANDA 74-771, for Cholestyramine for Oral Suspension, USP dated October 20, 1995. Reference is also made to your facsimile "Chemistry Comments to be Provided to the Applicant and Labeling Deficiencies", sent March 4, 1997. A copy of this facsimile has been included for your reference.

BNP is amending the application by responding to the numbered deficiencies and providing the supportive documentation as corresponding numbered exhibits.

RECEIVED

APR 7 1997

GENERIC DRUGS

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Chemistry Comments

Labeling Deficiencies:

The container labels and insert labeling have been revised as instructed by the Labeling Review Branch. Included in Exhibit 5 are:

Twelve (12) representative printed copies of the single dose packet container labeling;

Twelve (12) representative printed copies of the can container labeling;

Four (4) draft copies of the package insert.

It is noted that FDA reserves the right to request further changes in our labels and/or labeling. To facilitate review of this submission and in accordance with 21 CFR 314.94(a)(8)(iv), BNP has provided a side-by-side comparison of our proposed labeling in Exhibit 6.

Exhibit 7 contains a copy of the referenced March 4, 1997 facsimile from the Food and Drug Administration to BNP for your convenience..

I trust the information provided in this amendment will sufficiently answer your questions, but if additional information is required, please call me at (305) 575-6336.

Sincerely,



Steven M. Viti, Ph.D.

Associate Director, Regulatory Affairs

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Chemistry Comments

3/4/97

#30

CHEMISTRY REVIEW NO. 2

2. ANDA # 74-771

3. NAME AND ADDRESS OF APPLICANT
Baker Norton Pharmaceutical Inc. (BNP)
8800 N.W. 36th Street
Miami, FL 33178-2402

4. BASIS OF SUBMISSION
Adequate per CR # 1.

The listed drug products are Questran (eq 4 gm resin/packet) by Bristol Myers Pharmaceutical Laboratories approved in NDA # 16-640 001 (packet).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Cholestyramine For Oral Suspension, USP Powder

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

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 10-20-95

* Amendment: 6-13-96

* Major Amendment: 10-18-96 (Response to NA letter 4-18-96)

* NC (BIO): 11-27-96 (Response to bio letter dated 5-20-96)

FDA:

Accepted for filing Letter Date: 12-8-95

NA Letter (chemistry + Labeling): 4-18-96

Deficiency letter (BIO): 5-20-96

10. PHARMACOLOGICAL CATEGORY

1. Reduction of elevated serum cholesterol.

2. Relief of pruritus associated with partial biliary obstruction.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Powder (Oral)

14. POTENCY
4 g/Dose

15. CHEMICAL NAME AND STRUCTURE
NAME: Cholestyramine is a synthetic anion ion-exchange polymer in which quaternary ammonium groups are attached to a copolymer of styrene and divinylbenzene.

STRUCTURE: See CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. GENERAL COMMENTS:

1. Component and composition section became acceptable.
2. Reference is adequate per M. Shaikh's review dated 6-5-96.
3. Adequate information is submitted regarding manufacturing, testing and packaging facilities of the drug product.
4. Adequate information is submitted to support the all the container/closure system used the drug product.
5. Adequate data is submitted to support 24 months of expiration dating period for the drug product.
6. A revised EER need to be submitted in order to list the new address of the packaging facility (
7. FPL submitted in this amendment - pending review.
8. Bio review of firm response dated 11-27-96 is pending review.

B: COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments listed in section # 28, 29, 33 and 34.

Labeling comments will be communicated separately.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with a FAX amendment is being issued to the firm:

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
2-4-97
Revised on 2-20-97

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Chemistry Review

2

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 74-771
3. NAME AND ADDRESS OF APPLICANT
Baker Norton Pharmaceutical Inc. (BNP)
8800 N.W. 36th Street
Miami, FL 33178-2402
4. BASIS OF SUBMISSION
The listed drug products are Questran (eq 4 gm resin/packet) by Bristol Myers Pharmaceutical Laboratories approved in NDA # 16-640 001 (packet). Baker Norton submitted patent certifications for their applications certify that there are no listed patents for Cholestyramine Powder, Oral. Additionally, no exclusivity exists for these drug products according to 14th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluation. The proposed drug products contains the same active ingredient and has same strength, dosages form, route of administration, indications and usage as the listed drug.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
None used
7. NONPROPRIETARY NAME
Cholestyramine For Oral Suspension, USP Powder
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 10-20-95
Accepted for filing Letter Date: 12-8-95
10. PHARMACOLOGICAL CATEGORY
 1. Reduction of elevated serum cholesterol.
 2. Relief of pruritus associated with partial biliary obstruction.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Powder (Oral)

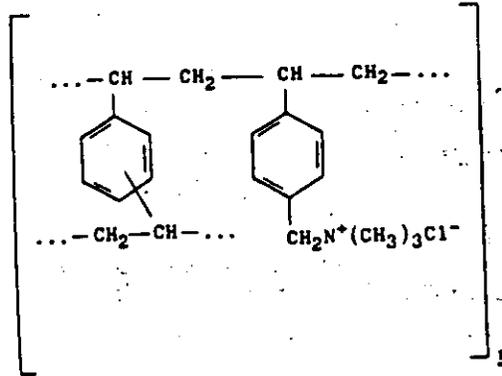
for

14. POTENCY
4 g/Dose

15. CHEMICAL NAME AND STRUCTURE

NAME: Cholestyramine is a synthetic anion ion-exchange polymer in which quaternary ammonium groups are attached to a copolymer of styrene and divinylbenzene.

STRUCTURE:



typified structure of main polymeric groups

16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. GENERAL COMMENTS:

1. Qualitative composition for the formulations listed in both ANDAs is not identical to that of the innovator's drug product.
2. Intended production batch size for all these ANDAs will be 700 kg.
3. Executed batch record of size kg for this ANDA submitted.
7. BNP will market this drug product into packet of 9 gm and canisters (From two manufacturer) containing 378 gm of Cholestyramine Powder for Oral suspension.
8. BNP packaged the entire executed batches into marketplace container/closure.
9. BNP submitted adequate information for in-process controls.
10. BNP's release specifications for the finished drug product are based on USP 23.
11. BNP submitted 3 months under accelerated conditions stability data and 3 and 6 months stability data at ambients temperature for all executed batches.
12. Samples will not be requested from BNP as the drug products are USP products.
13. Bio - review pending.

B: COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments listed in section # 20, 21, 22, 24, 26, 28, 29, 32, 33 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with a major amendment is being issued to the firm.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

2-26-96

Revised on 3-29-96 per Mike Smela's suggestions.

cc:

Endorsements:

HFD-625/M. Shaikh/
HFD-625/M. Smela/

A *JS* *rk* *4/16/96*
in
for smela 4/5/96

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F/T by:

Mujahid
Shaikh
4/4/96

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Chemistry Review #1