CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-771

CORRESPONDENCE

BAKER NORTON PHARMACEUTICALS, INC.

Facsimile 1-301-594-0180

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

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

July 1, 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

NDA ORIG AMENDMENT
FA

TELEPHONE AMENDMENT

Dear Mr. Sporn:

In reference to Baker Norton ANDA 74-771, Cholestyramine for Oral Suspension, USP Powder, 4 gram, we received a telephone request from Robert Smela and Mujahid Shaikh on June 30, 1997. We were requested to file a telephone amendment to the ANDA addressing the following two points, shown below in bold.

1) Update the active drug substance specification to include the OVI requirement included in Supplement 3, USP XXIII.

Included as Attachment 1 is a specification for the cholestyramine active drug substance, updated to include the OVI requirement as specified in Supplement 3, USP XXIII. Included in Attachment 2 is certification from the cholestyramine active drug substance supplier, Company, that of the chemicals listed in the OVI test (USP <467>), only is expected to be present in Cholestyramine based on their manufacturing process.

2) Clarify whether or not the new USP XXIII Supplement 6 "Exchange Capacity" method will be used for either the active drug substance or the finished drug product, or will the methods submitted in the ANDA continue to be used.

Active Drug Substance: The cholestyramine drug substance specification indicates that this test will be performed in accordance with the current USP. As this method has changed for the active drug substance in Supplement 6, Baker Norton intends to use the new USP exchange capacity method.

Finished Drug Product: The Cholestyramine for Oral Suspension, USP Powder (4 g Anhydrous Cholestyramine Packet and 42 Dose Can) specifications both indicate that the product will be tested for assay by the use of validated in-house method STP Although the USP has changed their method from that previously named Assay to that currently named Exchange Capacity, Baker Norton will continue to use the validated method that has been submitted, STP

I trust that information provided 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

RECEIVED
JUL 02 1997
GENERIC DRUGS

BAKER NORTON
PHARMACEUTICALS, INC.

Facsimile 1-301-594-0180

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

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

July 1, 1997

Douglas Sporn, Director
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Center for Drug Evaluation and Research
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7500 Standish Place, Room 150
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Sincerely,

Steven M. Viti, Ph.D.
Associate Director, Regulatory Affairs

BAKER NORTON PHARMACEUTICALS, INC.

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

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

29 May, 1997

FPL

FA

FPL insert submitted
6/4/97

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

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

Dear Mr. Sporn:

Enclosed please find labeling for 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 facsimile "Labeling deficiencies from April 3, 1997 submission as discussed via telephone. Submit as telephone amendment.", sent April 17, 1997. A copy of this facsimile has been included for your reference in Exhibit 1.

Labeling:
The insert labeling has been prepared as instructed by the Labeling Review Branch and is included in Exhibit 2:

Twelve (12) final printed package inserts

We have not included a side by side comparison because there have been no changes to the labeling since a side by side comparison was presented in earlier submissions. It is noted that FDA reserves the right to request further changes in our labels and/or labeling.

I trust that information provided 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

RECEIVED

MAY 30 1997

GENERIC DRUGS

BAKER NORTON PHARMACEUTICALS, INC.

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

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

14 May, 1997

ORIG AMENDMENT
NFA

FPL

=PL - not satisfactory
D+A missing
C. Holquist
5-20-97

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

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

Dear Mr. Sporn:

Enclosed please find labeling response 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 facsimile "Labeling deficiencies from April 3, 1997 submission as discussed via telephone. Submit as telephone amendment.", sent April 17, 1997. A copy of this facsimile has been included for your reference in Exhibit 1.

Labeling:
The carton labeling and insert labeling have been prepared as instructed by the Labeling Review Branch. Included in Exhibit 2 & 3 are:

Twelve (12) final printed package inserts
Twelve (12) representative printed copies of the carton labeling

We have not included a side by side comparison because there have been no changes to the labeling since the side by side comparisons were presented in earlier submissions. It is noted that FDA reserves the right to request further changes in our labels and/or labeling.

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

Sincerely,

Steven M. Viti

Steven M. Viti, Ph.D.
Associate Director, Regulatory Affairs

RECEIVED
MAY 15 1997
GENERIC DRUGS

ANDA 74-771

MAY 29 1997

Baker Norton Pharmaceuticals, Inc.
Attention: Steve Viti, Ph.D.
4400 Biscayne Blvd.
Miami FL 33137

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cholestyramine for Oral Suspension USP, 4 grams.

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

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

Sincerely yours,

/S/

5/28/1997

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

cc: acket

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez AOS 5/28

DRAFTED: STM 5/28/97 X:\WPFILE\BIO\FINAL\74771BIO.FAP

BAKER NORTON PHARMACEUTICALS, INC.

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

November 27, 1996

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

BIOAVAILABILITY
NEW CORRESP
NC Bio noted NAI Sirlufe 1/16/97

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 correspondence dated May 20, 1996, a copy of which is included for your reference.

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

1. **For the equilibrium binding studies you are advised to calculate the affinity (k_1) and capacity (k_2) for the total bile acid salts (GCA + GCDA + TDCA) using both the best fit Langmuir nonlinear equation (Equation 1 of the Guidance) and the linear equation (Equation 2 of the Guidance) for the test and the reference products. The 90% confidence intervals should be calculated for the k_2 values of total bile acid salt derived from the equilibrium studies without acid pretreatment of the resin.**

   The affinity (k_1) and capacity (k_2) for the total bile acid salts have been calculated using both the best fit Langmuir nonlinear equation (Equation 1 of the Guidance) and the linear equation (Equation 2 of the Guidance) for the test and reference products. The 90% confidence intervals have been calculated for the k_2 values of total bile acid salt derived from the equilibrium studies without acid pretreatment of the resin. The data are presented in **Exhibit 1**.

2. **Only mean data was presented (±SD) from the equilibrium and kinetics studies on its test and reference drug products. You should also submit the six individual % bound and millimoles bound per 10 mg resin values for the individual and**

12.26.96

combined bile acid salts, in addition to the mean (±SD) of the six values. This data should be submitted as a hard copy and on 3.5 inch diskette(s).

Individual observations for the six samples of the test and reference drug products are provided in **Exhibit 2** and on diskette (enclosed). These data have been revised in order to report all C_{eq} values below LOQ as zero.

3. **All standard curves and associated data should be submitted.**

Single-point calibration, suitable for the analysis of drug substances and products, was validated and used rather than repeated standard curves.

The chromatographic system was developed for its intended purpose and validated, with definition of the linear range of the system prior to use. The procedure specifies three operational details which insure that the entire range of concentrations in a binding equilibrium study are well within the defined linear range.

1. Samples are grouped by starting bile salt concentration, so that the range of concentrations in an analytical run is known.

2. Two injection volumes are specified, dependent upon initial bile salt concentration. Twenty microliters are injected of samples from experiments using concentrations below 3 mM, while 10 µL are injected of those above 3 mM.

3. The reference used in determining the extent of bile acid binding at each level is the initial bile salt solution. These solutions are prepared as standards and are the highest concentration in the run.

4. **In the kinetics studies, AUC values for binding of all three acids (GCA, TDCA, and GCDCA in molar ratios of 3:1:3) were determined. Please be advised that the use of this AUC parameter is inappropriate for establishing equivalence between the test and reference drug product.**

Baker Norton acknowledges the agency's comments.

5. **Chromatograms of the analysis of individual observations and chromatograms of blanks containing cholestyramine with no bile acid salt should be submitted for one-fifth of the runs chosen at random from each of the two equilibrium and two kinetics studies.**

Chromatograms of bile acid salts injected separately should be submitted to show that there were no significant bile acid salt contaminants interfering with the analysis of other bile salts.

The requested chromatograms are presented in **Exhibit 3** in the following manner :

Section A : One-fifth, or more, of the chromatograms for the 0.3 mM kinetic study;
Section B : One-fifth, or more, of the chromatograms for the 3.0 mM kinetic study;
Section C : One-fifth, or more, of the chromatograms for the equilibrium study without acid pre-treatment;
Section D : One-fifth, or more, of the chromatograms for the equilibrium study with acid pre-treatment;
Section E : Chromatograms of bile acid salts injected separately to demonstrate that there were no significant bile acid salts contaminants interfering with the analysis of other bile salts.

6. **Mean individual bile acid salt concentrations were reported which are less than your declared limits of quantitation (LOQ), e.g., TDCA and GCDCA concentration levels in the equilibrium studies (with acid pretreatment and no acid pretreatment) and the kinetics studies at the total bile acid salt concentration of 0.3 mM. If any of the non-zero values used in determining the mean values were less than the LOQ, you have the following choices: establishment of a lower LOQ; or recalculation of the reported mean values which were derived from nonzero individual values less than the LOQ. (The recalculation should treat these lower than LOQ values as zero). The chromatograms for the LOQ concentrations of each analyte should be provided.**

A LOQ of 0.01 mM GCA, TDCA and GCDCA was validated and is reported in **Exhibit 4**. The reported mean values and individual values were recalculated by treating all responses below LOQ as zero. The new k_1, k_2 and r^2 for both equilibrium studies are reported in Tables 1 and 2 in **Exhibit 4**.

7. **Satisfactory linearity, accuracy, and precision data should be submitted for concentrations down to the appropriate LOQ.**

The new LOQ established for the *in vitro* study is 0.01 mM for all three bile acid salts. The linearity, accuracy and precision data that establishes this new level of LOQ are presented in **Exhibit 5.**

8. **No stability data was submitted on the bile acid salt solutions. Stability testing should be done on filtrates of the three analytes to show they are stable under the time frame and conditions of the analytical methodology.**

As demonstrated by the following table the three bile acid salts are stable for 24 hours at 37°C, the conditions the bile acids are subjected to by the *in vitro* study. This data was generated by preparing the sample solutions at the specified bile salt concentrations in SIF pH 6.8 and 0.1 M NaCl from a common stock bile salt solution and placing in a water bath for 24 hours at 37°C. After 24 hours elapsed, the samples were removed, filtered and analyzed on the chromatograph along with standard bile salt solutions prepared at the same concentrations. The standard solutions were freshly prepared at the

time of analysis from the same stock solution as the sample solutions. The percent recovery was calculated by comparing the responses from the sample solution to that of the standard solutions.

	Percent Recovery after 24 hours at 37°C		
Sample Preparation	**GCA**	**TDCA**	**GCDCA**
1.0 mM in SIF pH 6.8	98.64%	98.32%	98.68%
10.0 mM in SIF pH 6.8	99.32%	99.23%	99.48%
1.0 mM in 0.1 M NaCl	100.46%	102.10%	100.74%
10.0 mM in 0.1 M NaCl	99.92%	99.32%	100.03%

9. **No content uniformity or assay data, or expiration date was reported on the reference product used in the study. This information should be supplied.**

Reference Product : Questran®
Lot Number : L4J56B
Expiration Date : 11/97
Potency : 98.4% LC
Content Uniformity : 92.0%
(n=10) 95.0%
97.5%
89.9%
94.1%
95.9%
97.9%
94.8%
91.5%
93.3%
Average : 94.2% LC
RSD : 2.74%
Range : 89.9% LC - 97.9% LC

10. **The test batch size should be a size intended to produce a net yield of at least 10 percent of the number of finished-dosage units proposed in the maximum-size production batch for which authorization is sought or 100,000 finished-dosage units, whichever is greater. Please refer to The Office of Generic Drugs, Policy and Procedure Guide #22-90, Bio-Batch Requirements Revised 9-13-90, for further information.**

Please explain why the batch size of was chosen while the above Guidance designates a minimum of 100,000 units. The number of finished-dosage units proposed in the maximum-size production batch for which authorization is sought should be supplied.

The proposed Production batch size will be identical in size to the test batch size of kilograms. This is the maximum amount that will be used for the future manufacture of Cholestyramine for Oral Suspension USP, Powder. Since each unit dose contains 9 grams of finished product, the maximum number of finished dosage units that can be produced is units.

Baker Norton Pharmaceuticals, Inc. trusts that we have responded satisfactorily to all the deficiencies cited. If any additional information is needed, please do not hesitate to contact me at (305) 575-6336.

Sincerely,

Steven M. Viti

Steve Viti, Ph.D.
Associate Director, Regulatory Affairs

enc. 3.5" diskette containing data for Exhibit 2

BAKER NORTON PHARMACEUTICALS, INC.

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

October 18, 1996

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

RE: ANDA #74-771 - Cholestyramine for Oral Suspension USP, (4 grams anhydrous Cholestyramine resin per packet and scoopful)

Dear Mr. Sporn,

Reference is made to our Abbreviated New Drug Application submitted on October 20, 1995, and OGD's review letter dated April 18, 1996. Baker Norton Pharmaceuticals Inc. hereby submits this Major Amendment in response to the Agency's comments. To facilitate review of this submission, each comment is reiterated below in bold type, followed by our complete response.

In our effort to address all open issues pertaining to the chemistry, manufacturing, controls and labeling portions of this application, we present the following :

A. Chemistry Deficiencies

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

10/18/96

To facilitate the agency's review of the revised labeling, **Exhibit 11** of this amendment contains side-by-side comparisons of the previous version of each component versus the updated version. Please note that all differences have been highlighted and annotated, as requested.

Additional Deficiencies

1. **Please submit the current available room temperature stability data for the executed batches, if available.**

   Updated room temperature stability reports for each package configuration are presented in **Exhibit 12** of this amendment.

2. **The cGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.**

   Baker Norton acknowledges that all firms referenced in the application must be cleared for satisfactory cGMP compliance prior to approval.

   Please note that our pre-approval inspection was conducted over the period of June 3 - 7, 11, 12, 14 / 96. On June 24, 1996, we received a letter from the local District Office which confirmed that our firm is in substantial compliance with cGMP regulations as they apply to this application.

3. **The analytical methods published in USP shall be considered official for regulatory purposes, and the procedures proposed in this ANDA shall be considered alternates. In case of a dispute, the results obtained by the USP method prevail.**

   Baker Norton acknowledges the fact that USP methods are the official methods for regulatory purposes and that results derived from these methods will prevail in the case of a dispute.

4. **Please be advised that OGD now accepts stability studies conducted at 25° ± 2°C/ 60 ± 5% RH per letter to ANDA/AADA applicants dated August 18, 1995. OGD will continue to accept any studies conducted at the condition it has recommended in the past (i.e., 25° - 30°C)/ ambient temperature.**

   Baker Norton acknowledges that the agency is currently accepting stability studies conducted under the two referenced sets of storage conditions.

Additionally, we wish to inform the agency that our contract packaging firm, a will be closing their Richmond, Virginia facility by the end of this year. The packaging operation is being relocated to ; facility at the following address:

:3

The acility is registered with the Food and Drug Administration under establishment registration # 2530802, and is covered by DMF An access letter to DMF ŧ s presented in **Exhibit 13** of this amendment. Please be advised that the packaging operations at the new facility will be executed using the same equipment and procedures as the existing facility. as engaged in extensive discussions with the agency regarding the relocation of the packaging facility. Copies of relevant agency correspondence are included in **Exhibit 14** of this amendment.

Please note that all commercial quantities of the packet configuration will be packaged at the new facility and stability studies will be conducted in accordance with the post-approval commitments defined in our ANDA. Our stability commitments extend above and beyond the requirements for the packaging site transfer that the agency defined in their correspondence to (i.e. we will study the first three commercial production batches as opposed to just one batch.) Results of the stability studies will be presented to the agency in our annual reports.

We believe that this information is sufficient to facilitate the agency's review and approval of the packaging site transfer.

This concludes our Major Amendment in response to the agency's letter of April 18, 1996. Baker Norton Pharmaceuticals Inc. trusts that you will find this submission complete and in order, and looks forward to the approval of our Abbreviated New Drug Application.

Sincerely,

Steve Viti, Ph.D.
Associate Director, Regulatory Affairs

ANDA 74-771

Baker Norton Pharmaceuticals, Inc.
Attention: Edgar W. Mitchell, Ph.D.
8800 N.W. 36th Street
Miami, FL 33178-2404

Dear Sir:

This is in reference to your abbreviated new drug application dated October 20, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cholestyramine for Oral suspension, USP, equivalent to 4 g resin per packet or scoopful.

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

A. Chemistry Deficiencies:

B. Labeling Deficiencies:

1. GENERAL COMMENT

Revise the established name on all labels and labeling to read as follows:

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP

2. CONTAINER

a. 9 g packet

i. Add the following:

Usual Dosage: See package insert.

ii. Storage Recommendations - Include the recommended temperature ranges based on your stability studies.

iii. Preparation - ...2 to 6 ounces...

b. 378 g can

i. GENERAL COMMENT

We encourage you to indicate on the scoop provided that it is not interchangeable with scoops for other products.

ii. Primary Panel

A) See comments under a. above.

B) Revise to read "g" rather than "G".

C) Relocate "Contents 378 g (168 g anhydrous cholestyramine)" to appear above in conjunction with "42 measured doses".

D) Place an asterisk (*) immediately following "scoopful" and immediately prior to the "Each level scoopful contains..." statement on the secondary panel.

iii. Secondary Panel

A) Relocate "This product contains sucrose." statement to the main panel.

B) Add the heading "Usual Dosage" before "See package insert...".

C) Revise to read:

*Each level scoopful...

3. CARTON (60 x 9 g packets)

a. See comments under CONTAINER.

b. Primary Panel

i. Relocate the expression of strength to appear directly below the established name and revise to read as follows:

4 grams...per packet*

ii. Add a picture of the packet as seen on the innovator's labeling.

iii. Add the following:

*Each packet contains 4 grams of anhydrous cholestyramine in 9 grams of Cholestyramine for Oral Suspension.

iv. Delete "Powder" from the title on the packet in all illustrations.

c. Top Panel

i. Insert "Usual Dosage" prior to "See package..." statement.

ii. The space allocated for the "Pharmacy Label" appears too small for a pharmacy label to be attached. Increase the amount of space.

d. Secondary Panel

See above comments regarding the established name and illustrations.

4. INSERT

a. TITLE

See comment under CONTAINER.

b. GENERAL COMMENT

Unless otherwise directed below, replace the full name, "Cholestyramine for Oral Suspension", with "cholestyramine resin" in all areas of the text of the insert except for the DESCRIPTION and HOW SUPPLIED sections.

c. DESCRIPTION

i. Paragraph 1, sentence 3 - Revise to read:

The cholestyramine resin in this product is not absorbed...

ii. Alphabetize the listing of inactive ingredients.

iii. Revise the last paragraph to read:

Cholestyramine for Oral Suspension USP, contains the...

d. CLINICAL PHARMACOLOGY

Insert the following text to appear as a subsection after the last paragraph:

Clinical Studies

In a large, placebo-controlled, multi-clinic study, LRC-CPPT[1], hypercholesterolemic subjects treated with cholestyramine resin had mean reductions in total and low-density lipoprotein cholesterol (LDL-C) which exceeded those for diet and placebo treatment by 7.2% and 10.4%, respectively. Over the seven-year study period the cholestyramine resin group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% cholestyramine resin and 8.6% placebo). The subjects included in the study were men aged 35 to 39 with serum cholesterol levels above 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to females and other segments of the hypercholesterolemic population.

Two controlled clinical trials have examined the effects of cholestyramine monotherapy upon coronary atherosclerotic lesions using coronary arteriography. In the NHLBI Type II Coronary Intervention Trial[2], 116 patients (80% male) with coronary artery disease (CAD) documented by arteriography were randomized to cholestyramine resin or placebo for five years of treatment. Final study arteriography revealed progression of coronary artery disease in 49% of placebo patients compared to 32% of the cholestyramine resin group ($p<0.05$), a 35% reduction of disease progression with cholestyramine resin treatment.

In the St. Thomas Atherosclerosis Regression Study (STARS)[3], 90 hypercholesterolemic men with CAD were randomized to three blinded treatments: usual care, lipid-lowering diet, and lipid-lowering diet plus cholestyramine resin. After 36 months, follow-up coronary arteriography revealed progression of disease in 46% of usual care patients, 15% of patients on lipid-lowering diet and 12% of those receiving diet plus cholestyramine resin ($p<0.02$). The mean absolute width of coronary segments decreased in the usual care group, increased slightly (0.003 mm) in the diet group and increased by 0.103 mm in the diet plus cholestyramine group ($p<0.05$). Thus, in

these randomized controlled clinical trials using coronary arteriography, cholestyramine resin monotherapy has been demonstrated to slow progression[2,3] and promote regression[3] of atherosclerotic lesions in the coronary arteries of patients with or at risk for coronary artery disease.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or intensive combination therapy using diet plus colestipol (an anion exchange resin with a mechanism of action and an effect on serum lipids similar to that of Cholestyramine for Oral Suspension) plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.

e. INDICATIONS AND USAGE

i. Items 1 and 2, sentences 1 - Retain the full name, Cholestyramine for Oral Suspension.

ii. Number 1 - Delete the second and third paragraphs and replace with the following text:

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

Prior to initiating therapy with cholestyramine resin, secondary causes of hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic

syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total cholesterol - [(TG/5) + HDL-C]

For TG levels > 400 mg/dl, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases cholestyramine resin may not be indicated.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm initial and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of cholestyramine resin therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of cholestyramine resin or adding other lipid-lowering agents in combination with cholestyramine resin should be considered.

Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	LDL-Cholesterol mg/dl (mmol/L) Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
**Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dl (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dl (≥1.6 mmol/L).

Cholestyramine resin monotherapy has been demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis. In addition, in the LRC-CPPT trial, cholestyramine resin therapy reduced the combined rate of coronary heart disease death and non-fatal MI.

f. PRECAUTIONS

i. General

A) Delete paragraph one.

B) Revise paragraph three to read:

...be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

C) Revise paragraph four to read:

...constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 5 to 7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4 to 6 weeks apart. Increased fluid intake and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by one dose/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at one to six doses/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with cholestyramine resin may aggravate hemorrhoids.

ii. Information for Patients

A) Last sentence - Retain the full name.

B) Add the following text as the last sentence:

Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

iii. Drug Interactions

A) Revise paragraph one to read:

...warfarin, thiazide diuretics (acidic),...preparations, estrogens and

progestins, and digitalis...sequestrant. Cholestyramine resin may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance...

B) Revise paragraph two to read:

...absorption of fat-soluble vitamins such as A, D, E and K. When...(or parenteral) forms of fat-soluble vitamins should be considered.

C) Revise paragraph three to read:

SINCE...CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS SHOULD...

iv. Carcinogenesis, Mutagenesis, Impairment of Fertility

A) Delete "and" from the subsection heading.

B) Revise the last sentence of paragraph two to read:

...above, a six-year post-trial follow-up analysis of the LRC-CPPT patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

v. Pregnancy

A) Revise the subsection heading to read:

Pregnancy: Teratogenic Effects, Pregnancy Category C

B) Hyphenate "fat-soluble".

vi. Pediatric Use - Revise to read:

A) ...in the pediatric population is limited...

B) Retain the full name.

g. ADVERSE REACTIONS

i. Paragraph 2 - Delete "dyspepsia".

ii. Paragraph 4 - Revise to read:

...took a cholestyramine for oral suspension product. One...

iii. Miscellaneous - Revise to read:

...dental caries, erosion of tooth enamel, tooth discoloration.

h. DOSAGE AND ADMINISTRATION

i. Paragraph 1 - Retain the full name throughout this paragraph and revise the last sentence to read:

...of administration is at mealtime...interference with...

ii. Paragraph 2 - Revise to read:

Cholestyramine for Oral Suspension should...

iii. Concomitant Therapy - Revise to read:

...evidence suggests...lovastatin, simvastatin, and fluvastatin.

i. HOW SUPPLIED

Include your storage temperature recommendations based on your stability data.

j. CLINICAL STUDIES - Delete this section.

k. REFERENCES - Revise this section to read:

1. The Lipid Research...

2. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. Circulation 1984;69:313-24.

3. Watts, GF, Lewis B, Brunt JNH, Lewis ES, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas

Atherosclerosis Regression Study (STARS). Lancet 1992;339:563-69.

4. National Cholesterol Education Program. Second Report of the Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994 Mar;89(3):1333-445.

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed container labels and draft carton labeling and insert labeling.

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 with your last submission with all differences annotated and explained.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Please submit the current available room temperature stability data for the executed batches, if available.

2. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

3. The analytical methods published in USP shall be considered official for regulatory purposes, and the procedures proposed in this ANDA shall be considered alternates. In case of a dispute, the results obtained by the USP method prevail.

4. Please be advised that OGD now accepts stability studies conducted at 25° - 2°C/ 60±5% RH per letter to ANDA/AADA applicants dated August 18, 1995. OGD will continue to accept any studies conducted at the condition it has recommended in the past (i.e., 25°-30°C)/ambient temperature.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the

bioequivalence portion of your application. If you have substantiaI disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

4/16/96

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

cc: ANDA 74-771
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/M.Shaikh/4/4/96 Mujahid Shaikh 4/16/96
HFD-625/S.Liu for M.Smela/4/8/96 M Smela 4/16/96
HFD-613/CZimmermann/D.Konigstein for/4-9-96 D Konigstein 4/12.96
HFD-617/SO'Keefe/4-11-96 S O'Keefe 4/16/96
HFD-617/JPhillips/4-10-96 J. Phillips 4/16/96
F/T by: bc/4/12/96
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Not Approvable - Major Amendment

ANDA 74-771

Baker Norton Pharmaceuticals, Inc.
Attention: Edgar W. Mitchell, Ph.D.
8800 N.W. 36th Street
Miami FL 33178

DEC 8 1995

Dear Sir:

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

NAME OF DRUG: Cholestyramine for Oral Suspension, USP

DATE OF APPLICATION: October 20, 1995

DATE OF RECEIPT: October 23, 1995

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

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

Should you have questions concerning this application contact:

Sheila O'Keefe
Consumer Safety Officer
(301) 594-0370

Sincerely yours,

/S/

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

BAKER NORTON PHARMACEUTICALS, INC.

8800 Northwest 36th Street
Miami, Florida 33178-2404
Telephone 305/590-2200
Facsimile 305/590-2252

505(b)(2)(B)(ii)
11/1/95
Clause

October 20, 1995

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

Reference: Cholestyramine for Oral Suspension, USP Powder
(4 grams Anhydrous Cholestyramine resin per packet and scoopful)
Original Abbreviated New Drug Application

Gentlemen:

Baker Norton Phamaceuticals, Inc. herewith submits an abbreviated new drug application (ANDA) for Cholestyramine for Oral Suspension, USP Powder pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act. This application contains the information required under 21 CFR § 314.94 of the final Abbreviated New Drug Application Regulations published in the Federal Register on April 28, 1992.

This ANDA refers to the listed drug, QUESTRAN® (Cholestyramine for Oral Suspension, USP) POWDER by Bristol Myers.

Cholestyramine for Oral Suspension, USP Powder has been developed at Baker Norton Pharmaceutical's manufacturing facility in accordance with 21 CFR 210 and 211.

Ownership of this ANDA will reside with Baker Norton Pharmaceuticals, Inc. This product will be manufactured by Zenith Goldline Pharmaceuticals, Inc.
Baker Norton Pharmaceuticals, Inc., and Zenith Goldline Pharmaceuticals, Inc. are both subsidiaries of IVAX Corporation.

The manufacturer of the drug substance used to produce the product is:

The required in-vitro bioavailability/bioequivalence study was conducted on Cholestyramine for Oral Suspension, USP Powder and Questran ® POWDER by Baker Norton Pharmaceuticals, Inc.,

The in-vitro study was conducted as outlined in the "Interim Guidance Cholestyramine Powder In Vitro Bioequivalence" by S.G.Nerurkar, H. Singh, S.V. Dighe, R.I. Williams of the Division of Bioequivalence in the Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. This study indicates that Cholestyramine for Oral Suspension, USP Powder is bioequivalent to Questran ® POWDER by Bristol Myers.

Cholestyramine for Oral Suspension , USP Powder is stable and a two year expiration dating is requested. The two year expiration dating for this product is supported by one, two and three months accelerated stability data (40°C/80% relative humidity) in cans and single unit dose packets proposed for marketing. The stability studies were conducted under the stability protocol that is in conformance with the current FDA stability guidelines.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED Sections) for Cholestyramine for Oral Suspension, USP Powder are the same as those for QUESTRAN® POWDER.

This ANDA is submitted in four volumes:

Volume I:	Section I through Section V
Volume II:	Section VI
Volume III:	Section VII -Section XII
Volume IV:	Section XIII-Section XXI

Please be advised that the word "Regular" has been used as a description for the product in the developmental stage of the product in various documents for clarity , but the product refered to in the ANDA is "Cholestyramine for Oral Suspension, USP Powder".

It is respectfully requested that this application be accepted for filing and approved in a timely manner. Please do not hesitate to contact me at (305) 590- 3368, if you have questions or require any additional information.

Sincerely,

Edgar W Mitchell

Ed Mitchell, Ph. D.
Vice President
Regulatory Affairs

IJN/ewm

Enclosures