Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

April 21, 1998

NAZ

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

NAZ
5/31/98

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Amendment - Notification of Patent Certification**

Dear Sir or Madam,

The purpose of this amendment is to supply to the Office the proper documentation regarding the listed U.S. Patent No. 5,674,850.

In accordance with 21 CFR 314.95(a) and (c), the patent holder (Ferring AB) and the holder of the approved application for the listed drug (Rhone-Poulenc Rorer) were notified of the patent certification filed by Bausch & Lomb on February 5, 1998. A copy of our February 5, 1998 correspondence is enclosed.

Accordingly, the attorney for Ferring AB and Rhone-Poulenc Rorer has notified us that they have decided not to take any action at this time with respect to this issue. A copy of the March 26, 1998 notification is enclosed.

We trust this information will satisfy all of the requirements of 21 CFR 315.95(e) and of the Office of Generic Drugs for patent certification. If additional information is needed, or there are any questions, please do not hesitate to contact me at 813-975-7786 or 813-975-7775.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

RECEIVED
APR 22 1998
GENERIC DRUGS

Nadine 4/22/98

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

June 23, 1998

BAUSCH & LOMB

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AM

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Minor Amendment**

Dear Sir or Madam,

The purpose of this amendment is to respond to the Agency's January 27, 1998 "not approvable" letter for the above referenced application. In that letter the Agency indicated that our response would be considered a Minor Amendment.

Specifically, we wish to notify the Agency that has responded, in a letter dated March 20, 1998, to deficiencies noted by FDA in their December, 1998 letter regarding D . A copy of the cover letter for that response is enclosed.

Bausch & Lomb Pharmaceuticals provided additional bioequivalence information for ANDA 74-830 in a correspondence dated June 17, 1998.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's January 27, 1998 letter. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph D. Hawkins

Joseph Hawkins
Manager,
Regulatory Affairs

Enclosure

RECEIVED
JUN 24 1998
GENERIC DRUGS

Mailed 6-25-98

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

July 16, 1998

NAE
8/6/98
NC

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Patent Certification Amendment**

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application to provide certification for a recently listed patent.

In accordance with 21 CFR 314.94 (a)(12)(i)(A)(4), we are providing a Paragraph IV Certification for U. S. Patent No. 5,763,407 filed by Ferring Pharmaceuticals. The signed certification is enclosed immediately following the 356h.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

RECEIVED
JUL 17 1998
GENERIC DRUGS

Made NC 7-23-98

ARNOLD & PORTER
555 TWELFTH STREET, N.W.
WASHINGTON, D.C. 20004-1202
(202) 942-5000
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DENVER
LOS ANGELES
LONDON

DONALD O. BEERS
(202) 942-5012

NAT Immediate 8/31/98

NEW CORRESP

NC

August 10, 1998

**VIA FEDERAL EXPRESS**

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration
HFD-600, Room 286
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

Re: ANDA No. 74-830

Dear Mr. Sporn:

We are writing on behalf of our client, Rhone-Poulenc Rorer, Inc., concerning the notice of certification of non-infringement sent by Bausch & Lomb Pharmaceuticals, Inc. to Rhone-Poulenc Rorer concerning desmopressin acetate nasal solution U.S.P., covered by ANDA No. 74-830. Bausch & Lomb originally sent a deficient notice to Rhone Poulenc Rorer that was received on July 21, 1998. In response to Rhone-Poulenc Rorer's assertion that that notice was insufficient to satisfy the requirements of the statute and regulations, Bausch & Lomb sent a subsequent notice. That was received on August 10, 1998. We enclose a date-stamped copy of the subsequent notice.

It is the position of Rhone-Poulenc Rorer that the 45-day period provided by Federal Food, Drug, and Cosmetic Act Section 505(j)(5)(B)(iii) during which no ANDA approval may issue, begins with the August 10 date of receipt of proper notice. We are sending this letter because Bausch & Lomb has asserted a different view, and we are concerned that it will not notify you of the second notice.

Sincerely,

Donald O. Beers

RECEIVED
AUG 11 1998

Enclosure

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

Called 9/16/98 to request return receipt copy or other proof of notification to the patent holder Nancy Mylund

**BAUSCH & LOMB**
Healthcare and Optics Worldwide

NEW CONNECT
NC

August 28, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Amendment - Notification of Patent Certification**

Dear Sir or Madam,

The purpose of this amendment is to supply to the Office the proper documentation regarding the listed U.S. Patent No. 5,763,407.

In accordance with 21 CFR 314.95(a) and (c), the patent holder (Ferring AB) and the holder of the approved application for the listed drug (Rhone-Poulenc Rorer) were notified of the patent certification filed by Bausch & Lomb on July 17, 1998. A copy of our July 17, 1998 correspondence is enclosed. A copy of the US Mail Return Receipt is also enclosed.

We trust this information will satisfy all of the requirements of 21 CFR 315.95(e) and of the Office of Generic Drugs for patent certification. If additional information is needed, or there are any questions, please do not hesitate to contact me at 813-975-7786 or 813-975-7775.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

RECEIVED
AUG 31 1998
GENERIC DRUGS

Nancy 9-9

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 313 975 7700 Fax 813 975 7770

December 1, 1998

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT
N/AF

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Labeling Amendment**

Dear Sir or Madam,

Reference is made to your facsimile communication of November 30, 1998 regarding the labeling for the above reference abbreviated new drug application. The purpose of this amendment is to reply to this communication and to provide the final printed labeling requested.

Regarding the "Rx Only" provision, we fully intend to include this in all labeling at a time when we can accomplish this in the container, carton and insert. At the next printing of these materials we will implement this change across the board.

Enclosed in this amendment are 12 final printed copies of the insert, as requested.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions or comments concerning this amendment, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

RECEIVED
DEC 0 2 1998
GENERIC DRUGS

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

December 15, 1998

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Telephone Amendment**

NC

Dear Sir or Madam,

Reference is made to the above reference abbreviated new drug application. The purpose of this amendment is to supply a letter from the patent holder's US agent regarding the status of the patent.

Enclosed in this amendment is a copy of a letter from the lawfirm of Hopgood, Calimafde, Kalil & Judlowe (the US agent for Ferring) which states that the 45-day clock has expired and Ferring will not sue Bausch & Lomb regarding patent 5,763,407.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions or comments concerning this amendment, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

Desk Copy: Peter Rickman
Office of Generic Drugs HFD-615

RECEIVED
DEC 16 1998
GENERIC DRUGS

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

January 4, 1999

BAUSCH & LOMB

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AM

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Telephone Amendment**

Dear Sir or Madam,

Reference is made to the above reference abbreviated new drug application, to our telephone amendment of December 30, 1998, and to telephone conversations with Mike Smela and Dr. Gene Shafer on January 4, 1999.

We hereby make the following commitments to the Agency regarding this application:

**A. Other Individual Chromatographic Related Substance:**

We hereby commit to revise our release specifications (Final Chemical Summary) and our stability specifications (Pre-marketed and Marketed Stability Protocols) to add an acceptance criteria for Other Individual Chromatographic Related Substance. The limit at release and on stability is set at Not More Than

**B. Impurity Peak Interference:**

We hereby commit to track and monitor the peak , at approximate . If the area % of this peak exceeds , we commit to performing a thorough investigation which shall include but not be limited to PDA analysis to identify the nature of the peak.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions or comments concerning this amendment, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

RECEIVED
JAN 06 1999
GENERIC DRUGS

Pharmaceuticals, Inc. 3500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

December 22, 1998

BAUSCH & LOMB

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC to AM

**Re: ANDA 74-830**
**Desmopressin Acetate Nasal Solution, 0.01%**
**Facsimile Amendment**

Dear Sir or Madam,

Reference is made to the above reference abbreviated new drug application and to your facsimile communication of December 21, 1998.

The following is a point-by-point response to the deficiencies delineated in the facsimile:

**A.1.a.** Reference is made to your statement:

*"Deficiencies*

1. *In reference to the June 17, 1998 amendment, the following questions and concerns pertain to the new . 5, pages 2 038 to 2 055; the release and stability specifications for the final product, pages 2 297 to 2 300 and 2 316 to 2 324, respectively; and the validation report for pages 2 339 to 2 392.*

   a. *What are your plans for the use of and be phased our for Chromatographic Related Substances, and retained only for the assay of Desmopressin Acetate and Chlorobutanol in the final product? Since more advanced than , we expect 5 to be designated the regulatory method. If this is not your intention, please justify."*

**Response:**

We acknowledge the reviewer's comments from A.1.a. to A.1.j. relating to the methods.

001 GENERIC DRUG

Page(s) 7

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

Nichols

Page(s) 2

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

Chemistry

16. Please submit updated stability data for this product.

B. Labeling Deficiencies

1. CARTON (1 x 5 mL)

Relocate "IMPORTANT: Pharmacist..." statement to appear on the main panel and boxed.

2. INSERT

I. PROFESSIONAL INSERT

a. GENERAL COMMENT

Revise to read "desmopressin acetate" rather than "Desmopressin acetate nasal solution" throughout the text of the insert, except in the DESCRIPTION, INDICATIONS AND USAGE, HOW SUPPLIED sections and where noted below.

b. DESCRIPTION

i. Revise paragraph one (first sentence) to read as follows:

Desmopressin Acetate Nasal Solution 0.01%, for intranasal use is an...analog of the natural pituitary hormone 8-arginine vasopressin (ADH).

ii. Revise the molecular weight to read "1183.32" rather than "1183.2".

c. CLINICAL PHARMACOLOGY

Paragraph one and paragraph two (second sentences) - Insert "intranasal" prior to "desmopressin acetate".

d. INDICATIONS AND USAGE

Revise the penultimate paragraph to read:

...to intranasal desmopressin acetate can...

e. CONTRAINDICATIONS

Revise to read:

Desmopressin acetate nasal solution is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin

acetate nasal solution.

f. PRECAUTIONS

i. Insert "intranasal" prior to "desmopressin acetate" in the following places:

General, paragraph one - First sentence.

Central Cranial Diabetes Insipidus - First sentence.

Drug Interactions

Pediatric Use, Primary Nocturnal Enuresis - Third sentence

ii. Laboratory Tests - ...osmolality measurements may...

iii. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise to read:

There have been no long-term studies in animals to assess the carcinogenic, mutagenic, or impairment of fertility potential of desmopressin acetate.

iv. Pregnancy Category B - Revise to read:

Reproduction studies performed in rats and rabbits by the subcutaneous route at doses up to 10 mcg/kg/day have revealed no evidence of harm to the fetus due to desmopressin acetate. This dose is equivalent to 10 times (for Factor VIII stimulation) or 38 times (for diabetes insipidus) the systemic human dose based on $mg/M^2$ surface area.

There are no adequate and well-controlled studies in pregnant women. Several publications of desmopressin acetate's use in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low birth weight babies. However, no causal connection between these events and desmopressin acetate has been established. A 15-year, Swedish epidemiologic study of the use of desmopressin acetate in pregnant women

with diabetes insipidus found the rate of birth defects to be no greater than that in the general population. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no uterotonic action and the physician will have to weigh the therapeutic advantages against the possible risks in each case.

v. Nursing Mothers - Revise to read:

...10 mcg. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to a nursing woman.

vi. Pediatric Use, paragraph one, second sentence - ...with intranasal desmopressin acetate in...

g. ADVERSE REACTIONS

i. Paragraph one - ...high dosages of intranasal desmopressin acetate have...

ii. Chart - Replace "DDAVP" with "Desmopressin Acetate".

iii. Insert the following text as the last paragraph in this section:

See WARNINGS for the possibility of water intoxication and hyponatremia.

h. OVERDOSAGE

...antidote for desmopressin acetate or desmopressin acetate nasal solution.

i. DOSAGE AND ADMINISTRATION

i. Primary Nocturnal Enuresis, last sentence - ...with intranasal desmopressin acetate in primary...

ii. Central Cranial Diabetes Insipidus - Revise paragraph one to read:

...well to intranasal desmopressin acetate. The usual...by a single daily dose of desmopressin acetate

administered intranasaly.

j. HOW SUPPLIED

See comment under CONTAINER.

II. PATIENT INSTRUCTION INSERT

a. Include the following text after the established name and strength:

A better way to deliver Desmopressin Acetate Nasal Solution.

Delivering Desmopressin Acetate Nasal Solution more efficiently.

Your doctor has prescribed desmopressin acetate as antidiuretic hormone replacement therapy. Follow the dosage schedule that is specified. The convenient nasal spray pump provides an efficient, reliable way to administer your medication. It is important, however, to adhere completely to the following instructions so that you will always receive a consistent dose of your medication.

b. We note, your comments regarding the additional information you have provided regarding the instructions for use. However, 21 CFR 314.94(a)(8)(iv) requires that your proposed labeling be the same as the reference listed drug, except for certain changes described in this regulation. In addition, all differences are to be annotated and explained in your side-by-side comparison. We note significant differences between your labeling and that of the reference listed drug, in particular in the instruction to the patient for priming and using the product. However, no explanation, other than you have "chosen to include more detailed instructions"' is provided. Please submit more detailed explanation of the differences. Please note, that if your proposed labeling contains clinically significant differences, such as instructions to use other medications, please provide us supporting data for these proposals.

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed container labels, carton 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 of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

A. Since neither the drug substance nor the drug product is covered by a compendial monograph, we will request verification of your analytical methods by an FDA laboratory.

B. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

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 substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/20/96

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

cc: ANDA #74-830
ANDA #74-830/DUP/Division File
Field Copy
HFD-600/Reading File

Endorsements: E J Schaefer 8/16/96

HFD-627/E.Schaefer, Ph.D./5-31-96, 6-21-96, 8-9-96
HFD-613/C.Holquist/6-21-96
HFD-613/A.Vezza for J.Phillips/6-21-96
HFD-627/P.Schwartz, Ph.D./5-21-96, 8-12-96 DS 8/16/96
HFD-617/W.Russell, CSO/6-18-96
X:\NEW\FIRMSAM\BAUSCH\LTRS&REV\74830NA1.LF
F/T by MM August 16, 1996
Not Approvable - Major

separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

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

cc: ANDA #74-830
ANDA #74-830/DUP/Division File
Field Copy
HFD-600/Reading File

E.F. Schaefer 7/2/96

Endorsements:

HFD-627/E.Schaefer/5-31-96, 6-21-96
HFD-613/C.Holquist/6-21-96 C. Holquist 7/2/96
HFD-613/A.Vezza for J.Phillips/6-21-96 P/S 7/2/96 A Vezza 7-5-96
HFD-627/P.Schwartz, Ph.D./5-21-96
HFD-617/R.Russell, CSO/6-18-96 R Russell 8/16/96 Russell for W. Russell 7/8/96
X:\NEW\FIRMSAM\BAUSCH\LTRS&REV\74830NA1.LF
F/T by MM July 2, 1996
Not Approvable - Major

W. ~~or B~~