CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-830

MICROBIOLOGY REVIEW(S)

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

July 25, 1996

A. 1. ANDA: **74-830**

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.
Attention: Peter Stoelzle
8500 Hidden River Parkway
Tampa, FL 33637

2. PRODUCT NAME: **Desmopressin Acetate Nasal Solution**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

A **0.01%** non-sterile nasal solution, which is packaged as a 5 mL fill in a 6 cc amber glass vial; one fully assembled unit consists of a pump, actuator with cover and the bottle of nasal solution. Each actuation delivers 0.1 mL (10 mcg) of the subject drug product

4. PRINCIPLE INDICATIONS: Management of primary nocturnal enuresis and as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region

5. PHARMACOLOGICAL CATEGORY: Antidiuretic hormone

B. 1. DATE OF INITIAL SUBMISSION:

December 31, 1995 (Received by OGD on 1/3/96)
- Subject of this review

2. DATES OF AMENDMENTS: N/A; no amendments containing sterility assurance information were submitted by the time of this review

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: July 25, 1996

C. REMARKS: The information provided in the application was sufficient to determine that the applicant is taking the necessary steps to ensure the microbial quality of the subject drug product (Desmopressin Acetate Nasal Solution, USP, 0.01%).

D. CONCLUSIONS: The submissions are therefore recommended for approval on the basis of microbial quality. Specific comments are provided in "E. Review Notes".

/S/

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 7/25/96 Received 7/25/96

cc:

Page(s) 1

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

Microbiologist #1 review notes, 7/25/96

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

August 1, 1997

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

NDA ORIG AMENDMENT
N/F

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

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's facsimile communication, dated July 29, 1997, for the above referenced application.

To facilitate your review, each of the observations and our corresponding response is provided below. Necessary supportive documentation is also provided for each response in the Attachments. An index with the attachment numbers, contents, and corresponding page numbers in this amendment is provided for your reference.

Reference is made to your observations:

Page(s) 3

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

Methods

A.4 The response 13.b is inadequate. The problems with the graph on page 1365 have not been resolved. It appears that the graph was plotted from results which were different from those in the table because the slope and intercept on page 1365 are different from those on either the original page 1364 or the revised page 1364. The duplication of values on the concentration axis (0.1, 0.1, 0.02, 0.02, etc.) doesn't make sense, and the concentration values of the plotted points do not seem to match those in the table. Such problems are not observed on pages 1446 and 1447.

Response: As noted by the reviewer, the graph on page 1365 is incorrect. A corrected graph was prepared but inadvertently omitted from our response to referenced question. Copies of the corrected graph and the table are provided in Attachment A.4. The duplicate values on the concentration axis of the graph have been eliminated and the graphed concentration values now correspond with the data presented in the table.

B. In addition to responding to the deficiencies presented above, please note that the formulation and labeling of the reference listed drug (RLD) have been changed to include a new preservative buffer system with corresponding changes in the labeled storage of the product. Please refer to the June 17, 1997, telephone conversation with Joseph Buccine of the Agency and Joseph Hawkins of Bausch & Lomb Pharmaceuticals. As discussed, it was recommended that the firm consider reformulating this product. In addition, Bausch & Lomb was advised to petition the Agency per 21 CFR 314.122 to determine whether the RLD's formulation was withdrawn for safety or effectiveness reasons.

Response:

1. Consideration of Reformulation of the Drug Product

Bausch & Lomb Pharmaceuticals (BLP) commits to reformulating Desmopressin Acetate Nasal Spray to obtain room temperature storage conditions, and will keep the Agency informed.

2. Citizen's Petition per 21 CFR 314.122

Bausch & Lomb Pharmaceuticals acknowledges the advise to pursue the filing of a Citizen's Petition as requested by the Agency. We will be addressing this issue in separate correspondence, and will commit to proceed to cause such a petition to be filed, if deemed necessary.

Labeling Deficiencies:

1. CONTAINER (5 mL Bottle)

Satisfactory

2. CARTON (5 mL Bottle)

Satisfactory

3. INSERT

Due to the changes in the labeling of the listed drug, (DDAVP Nasal Spray; Rhone-Poulenc Rorer Pharmaceutical Corp.; approved in draft August 7, 1996), revise your insert labeling as follows:

a. DESCRIPTION

Revise the molecular weight to read, 1183.34.

Response: The insert labeling was revised as requested. See the line indicated by (1) on the insert labeling copy provided in Attachment C.

b. CLINICAL PHARMACOLOGY

Revise the first sentence to read,
Desmopressin acetate is a synthetic analog of the...

Response: The insert labeling was revised as requested. See the line indicated by (2) on the insert labeling copy provided in Attachment C.

c. WARNINGS

Revise the first sentence of WARNING #2 to read,
...be adjusted downward in order...

Response: The insert labeling was revised as requested. See the line indicated by (3) on the insert labeling copy provided in Attachment C.

d. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility

Revise to read,
Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Response: The insert labeling was revised as requested. See the line indicated by (4) on the insert labeling copy provided in Attachment C.

ii. Pregnancy-Category B

Revise the fourth sentence of the last paragraph to read,
...the general population; however, the statistical power of this study is low.

Response: The insert labeling was revised as requested. See the line indicated by (5) on the insert labeling copy provided in Attachment C.

iii. Nursing Mothers

Revise the last sentence to read,
...to a nursing woman.

Response: The insert labeling was revised as requested. See the line indicated by (6) on the insert labeling copy provided in Attachment C

e. ADVERSE REACTIONS

Revise the first sentence of the second paragraph to read, ...lists the percentage of...

Response: The insert labeling was revised as requested. See the line indicated by (7) on the insert labeling copy provided in Attachment C.

f. OVERDOSAGE

Revise the first sentence so that "ADVERSE REACTIONS" appears in all capital letters.

Response: The insert labeling was revised as requested. See the line indicated by (8) on the insert labeling copy provided in Attachment C.

g. DOSAGE AND ADMINISTRATION (Central Cranial Diabetes Insipidus)

i. Revise the fourth sentence of the first paragraph to read, ...0.4 mL daily, as a single dose or divided into two or three doses.

Response: The insert labeling was revised as requested. See the line indicated by (9) on the insert labeling copy provided in Attachment C.

ii. Revise the penultimate sentence of the first paragraph to read, For children...

Response: The insert labeling was revised as requested. See the line indicated by (10) on the insert labeling copy provided in Attachment C.

iii. Revise the ultimate sentence of the first paragraph to read, ...daily dose of intranasal desmopressin acetate.

Response: The insert labeling was revised as requested. See the line indicated by (11) on the insert labeling copy provided in Attachment C

iv. Revise to add the following as the last paragraph:

The spray pump must be primed prior to the first use. To prime pump, press down four times. The bottle will now deliver 10 mcg of drug per spray. Discard intranasal desmopressin acetate after 50 sprays since the amount delivered thereafter per spray may be substantially less than 10 mcg of drug.

Response: The insert labeling was revised as requested. See the line indicated by (12) on the insert labeling copy provided in Attachment C.

In addition, we have added a scissors icon to the line between the package insert and patient instructions to indicate the manner in which the instructions are to be detached.

Please revise your package insert labeling, as instructed above, and submit in final print.

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

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

Response: The labeling has been revised as requested. Twelve (12) final printed package insert labeling are provided with this amendment.

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 August 21, 1996 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph Hawkins
Manager,
Regulatory Affairs

Enclosure

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

BAUSCH & LOMB
Healthcare and Optics Worldwide

August 25, 1997

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

ORIG AMENDMENT
N/A

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

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's telephone communication, dated August 19, 1997, for the above referenced application. In That communication, the Agency requested that we revise our carton labeling to include the following statement in prominent type on the front panel:

"KEEP REFRIGERATED AT 2° - 8°C (36° - 46°F)."

The labeling has been revised as requested and 12 copies of color artwork are enclosed.

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 August 21, 1996 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 Hawkins
Manager,
Regulatory Affairs

Enclosure

RECEIVED
AUG 26 1997
GENERIC DRUGS

Pharmaceutical Division | 3500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

September 12, 1997

BAUSCH & LOMB
Healthcare and Optics Worldwide

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

NEW CORRESP

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

Dear Sir or Madam:

The purpose of this correspondence is to responded to a request by the Agency's Mr. Joe Buccine with regard to the above referenced application.

As requested by the Agency, Bausch & Lomb Pharmaceuticals commits to cooperate with the Food and Drug Administration as necessary to resolve any methods issues which may be revealed when the Agency's evaluation of our methods validation work is completed.

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,

Joseph B. Hawkins
Manager,
Regulatory Affairs

SEP 15 1997