CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-830

CHEMISTRY REVIEW(S)

Page(s) 2

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

Chemistry #30, 7/29/97

Page(s) 1

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

#38, Chemistry 1/27/95

Page(s) 3

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

Chemistry, #38, 12/21/98

1. CHEMISTRY REVIEW NO. 5 Cycle #4

2. ANDA # 74-830 **FIRST GENERIC FOR THIS DOSAGE FORM OF THIS DRUG PRODUCT**

3. NAME AND ADDRESS OF APPLICANT

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Donald H. Chmielewski
8500 Hidden River Parkway
Tampa, FL 33637

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Desmopressin Acetate

13. DOSAGE FORM
Nasal Solution

14. STRENGTH
0.01%

4. LEGAL BASIS FOR SUBMISSION

The RLD is DDAVP® Nasal Spray, NDA 17-922, by Rhone-Poulenc Rorer.

Volumes 5.1 and 6.1 contain NC and faxes re new patent issues. The 45 day waiting period has expired, and Ferring will not sue re 5,763,407 (NC 12/15/98, Vol. A7.1). Peter Rickman informed me by E-mail on 12/16/98 that patent issues are resolved.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1-1.4:

12/31/95 Original ANDA
05/20/96 Bio "no further questions" letter
07/25/96 Micro acceptable
08/21/96 NA letter--chem & labeling, end of 1st cycle

Vol. A2.1:

11/07/96 Response to NA letter

Vol. A3.1:

02/28/97 Gratuitous amendment: Responses and attachments 1, 11, and 15 replace those in the amendment of 11/7/96.

07/29/97 Deficiencies were faxed to B&L (End of Cycle 2).
07/31/97 Fax from B&L re formulation change
08/01/97 Minor amendment in response to agency's fax
08/25/97 Labeling telephone amendment
09/09/97 ANDA Approval Summary
★ 09/12/97 NC--**B&L commitment to cooperate with FDA re MV issues.**
01/27/98 Chem fax re Bio and deficiencies (End of 3rd cycle)

Vol. A4.1-4.3:

11/04/97 Bio telephone amendment, in response to request of 10/27/97
01/13/98 Telecon between Bio and B&L re in vitro testing recommendations
01/21/98 Bio deficiencies were faxed to B&L.

Vol. A5.1:

01/26/98 NC—Bio: See Container section of chemistry review #4.

02/04/98 NC--Patent Certification
04/20/98 Fax from B&L re patent
04/21/98 NC--Patent Certification

Vol. A6.1-6.8:

★ 06/17/98 NC--Bio amendment in response to fax of 1/21/98, listed above, and to fax of 2/23/98, not in the jacket: Includes CMC info, Vol. A6.2, pages 2 039 to 2 055, and Attachments B and C. See ☞ under Points 23.A&B, 28.A&B, and 29 below.
09/22/98 Bio deficiencies were faxed to B&L.

★ 06/23/98 Telecon from Mike Smela to B&L, and Minor Amendment from B&L
★ 12/18/98 Chem Review #4, Cycle #4, of amendments of 6/17 and 6/23/98
★ 12/18/98 Revised EER--Facilities are acceptable.

07/16/98 NC--Patent Certification
08/10/98 NC--Patent Certification
08/28/98 NC--Patent Certification
09/04/98 Fax from B&L re patent
09/22/98 Fax from B&L re patent

Vol. A7.1-7.3:

	10/06/98	Bio and Labeling amendment in response to fax of 9/22/98
	11/30/98	Labeling deficiencies faxed to B&L
	12/01/98	Labeling amendment
	12/03/98	Bio "No further questions" letter and accompanying review
	12/07/98	Labeling Approval Summary
	12/15/98	NC re patent--Ferring will not sue re 5,763,407.
★	12/21/98	Chem NA fax, corresponding to Chem Review #4, Cycle #4, Vol. A6.1, re amendment of 6/17/98.
★	12/22/98	Facsimile amendment
	12/30/98	Telecon from Schaefer & Smela to B&L re fax amendment
	12/30/98	Telephone amendment
	01/04/99	B&L Telecons from Schaefer/Cai and to Schaefer/Smela re telephone amendment
	01/04/99	Telephone amendment
	01/11/99	Received MV report from DTAAD: All methods are acceptable for quality control and regulatory purposes.

☞ The CMC information in the amendment of 6/17/98 consists of two parts:

- A second exhibit lot, #025901, was manufactured for use in *in vitro* BE testing. Vol. A6.2, Attachment B, contains executed batch records; results from testing of raw materials, container components, and final product; and stability data, all for lot #025901.

  Attachment B also includes updated stability data for the exhibit batch in the original ANDA, #683601.

- A new [redacted] was presented in Vol. A6.2, pages 2 039 to 2 055. This method has been and will be used for content uniformity testing (quantity delivered per spray) during in-vitro bioequivalence studies, and for cleaning validation. The validation report is in Attachment C of that volume.

5. SUPPLEMENT(s)
N/A

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

10. PHARMACOLOGICAL CATEGORY

Antidiuretic hormone for the management of primary nocturnal enuresis, central cranial diabetes insipidus, or temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. A synthetic analogue of 8-arginine vasopressin.

11. Rx or OTC Rx

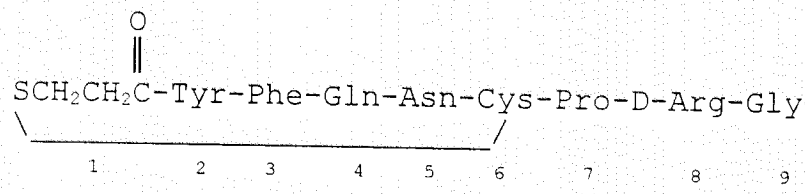
12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

$C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$. 1183.32 *CAS-62357-86-2*

Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine, monoacetate (salt), trihydrate;

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate (salt) trihydrate.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All CMC deficiencies have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

Ken Muhvich, Ph.D., **recommended approval** of ANDA 74-380 **on the basis of microbial quality** on 7/25/96.

31. SAMPLES AND RESULTS

MV was requested from STL 9/4/97.

On 09/12/97 B&L submitted a commitment to cooperate with FDA re MV issues.

I received a report from Dr. Henry Drew on 1/11/99. The methods are **satisfactory.**

32. LABELING

Teresa Watkins recommended approval 12/7/98.

33. ESTABLISHMENT INSPECTION

In EES, the overall recommendation is acceptable by M. Egas on 2/20/98.

34. BIOEQUIVALENCE STATUS

"No further questions" 12/3/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 74-830 can be APPROVED.

19.

REVIEWER:	DATE COMPLETED:	Revised:
Eugene L. Schaefer, Ph.D.	1/5/99	1/19/99

Endorsed by M.Smela

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Chemistry, #20 - #37, 1/19/99

1. CHEMISTRY REVIEW NO. 4 Cycle #4

2. ANDA # 74-830 **FIRST GENERIC FOR THIS DOSAGE FORM OF THIS DRUG PRODUCT**

3. NAME AND ADDRESS OF APPLICANT

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Donald H. Chmielewski
8500 Hidden River Parkway
Tampa, FL 33637

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Desmopressin Acetate

13. DOSAGE FORM
Nasal Solution

14. STRENGTH
0.01%

4. LEGAL BASIS FOR SUBMISSION

★ The RLD is DDAVP® Nasal Spray, NDA 17-922, by Rhone-Poulenc Rorer. At the end of the third Chem cycle, 1/27/98, there were no patent or exclusivity issues.

Since then, Volumes 5.1 and 6.1 contain NC and faxes re new patent issues. Peter Rickman informed me by E-mail on 12/16/98 that patent issues are resolved. From previous conversations, there will be a 45 day waiting period, so the ANDA will not be ready for approval until the middle or end of January.

★ Originally the RPR product had been labeled for storage in a refrigerator (2°-8°C). However, on 8/7/96 RPR received approval to market a new formulation containing a new preservative and buffer system, with a revised storage condition at RT.

In a NC dated 11/1/96 B&L requested a regulatory opinion re how the change in the RLD would affect the approval of ANDA 74-830.

This issue was addressed in an internal meeting on 7/17/97, attended by Gordon Johnston, Doug Sporn, Joseph Buccine and others. Please refer to the attached telecon record.

After the meeting, Mr. Buccine informed B&L that OGD was willing to proceed with the review process provided the innovator's reason for changing the formulation did not involve safety or efficacy concerns. He advised B&L to file a Citizen's Petition under 21 CFR 314.122, and to reformulate to match the RLD's new formulation. B&L replied they were already developing the new formulation and planned to file a supplement.

In a minor amendment of 8/1/97 (page 6 of cover letter), B&L committed to reformulating their product to obtain RT storage conditions. ANDA 74-830 will continue to be reviewed vs. the innovator's old formulation.

In a series of internal E-mails from 7/17 to 7/25/98, NDE informed OGD the refrigerated formulation had not been withdrawn from the market by RPR for safety or efficacy reasons, and that RPR had demonstrated bioequivalence between its refrigerated and RT formulations.

At the behest of the Office of Chief Counsel, OGD requested a formal determination from the Division of Metabolism and Endocrine Drug Products (memo from Mr. Douglas L. Sporn through Dr. James M. Bilstead to Dr. Soloman Sobel, 8/6/97, attached). A memo of 10/28/97, signed by Dr. Sobel and others, confirmed there were no safety of effectiveness issues responsible for the [formulation] change.

The determination was published as a Federal Register Notice on Friday, 11/21/97 (Vol. 62, No. 225, page 62322).

Doug Sporn and others have decided the commitment to reformulate is not relevant for the approval of this ANDA. See E-mails from 11/30/98 to 12/2/98.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1-1.4:

12/31/95 Original ANDA
05/20/96 Bio "no further questions" letter
07/25/96 Micro acceptable
08/21/96 NA letter--chem & labeling, end of 1st cycle

Vol. A2.1:

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08/25/97 Labeling telephone amendment
09/09/97 ANDA Approval Summary
09/12/97 NC--B&L **commitment** to cooperate with FDA re MV issues.
01/27/98 Chem fax re Bio and deficiencies (End of 3rd cycle)

Vol. A4.1-4.3:

11/04/97 Bio telephone amendment, in response to request of 10/27/97
01/13/98 Telecon between Bio and B&L re in vitro testing recommendations.
01/21/98 Bio deficiencies were faxed to B&L.

Vol. A5.1:

01/26/98 NC--Bio. See Container section of this chemistry review.

02/04/98 NC--Patent Certification
04/20/98 Fax from B&L re patent
04/21/98 NC--Patent Certification

Vol. A6.1-6.8:

★ 06/17/98 NC--Bio amendment in response to fax of 1/21/98, listed above, and to fax of 2/23/98, not in the jacket: **Includes** , Vol. A6.2, pages 2 039 to 2 055, and Attachments B and C--**The primary subject of this review.** See ☞ under Points 23.A&B, 28.A&B, and 29 below.
09/22/98 Bio deficiencies were faxed to B&L.

★ 06/23/98 Telecon from Mike Smela to B&L, and Minor Amendment from B&L--The authorization for this review

07/16/98 NC--Patent Certification
08/10/98 NC--Patent Certification
08/28/98 NC--Patent Certification
09/04/98 Fax from B&L re patent
09/22/98 Fax from B&L re patent

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10/06/98 Bio and Labeling amendment in response to fax of 9/22/98
11/30/98 Labeling deficiencies faxed to B&L
12/01/98 Labeling amendment
12/03/98 Bio "No further questions" letter and accompanying review
12/07/98 Labeling Approval Summary

☞ The CMC information in the amendment of 6/17/98 consists of two parts:

- A second exhibit lot, #025901, was manufactured for use in *in vitro* BE testing. Vol. A6.2, Attachment B, contains executed batch records; results from testing of raw materials, container components, and final product; and stability data, all for lot #025901.

  Attachment B also includes updated stability data for the exhibit batch in the original ANDA, #683601.

- A new is presented in Vol. A6.2, pages 2 039 to 2 055. This method is said to be used for content uniformity testing (quantity delivered per spray), but has been validated only for determination of Desmopressin related substances for release and stability of the final product. The validation report is in Attachment C.

5. SUPPLEMENT(s)
N/A

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

10. PHARMACOLOGICAL CATEGORY

Antidiuretic hormone for the management of primary nocturnal enuresis, central cranial diabetes insipidus, or temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. A synthetic analogue of 8-arginine vasopressin.

11. Rx or OTC Rx

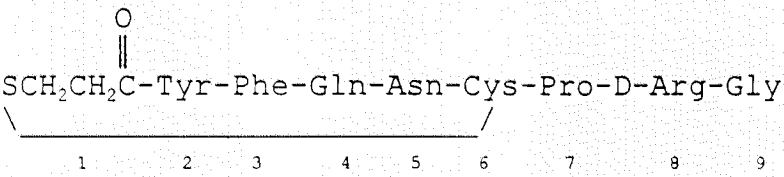
12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

$C_{48}H_{68}N_{14}O_{14}S_2 \bullet 3H_2O$. 1183.32 *CAS-62357-86-2*

Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine, monoacetate (salt), trihydrate;

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate (salt) trihydrate.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are deficiencies in Points 28.B and 29.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

Ken Muhvich, Ph.D., **recommended approval** of ANDA 74-380 **on the basis of microbial quality** on 7/25/96.

31. SAMPLES AND RESULTS

MV was requested 9/4/97. A report has not been received, as of 12/16/98. MV might need to be requested for a new

32. LABELING

Teresa Watkins recommended approval 12/7/98.

33. ESTABLISHMENT INSPECTION

In EES, the overall recommendation is acceptable by M. Egas on 2/20/98.

34. BIOEQUIVALENCE STATUS

"No further questions" 12/3/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 74-830 is **not approved--facsimile** amendment requested.

Usually a telephone amendment is requested after review of a minor amendment. However, in this case, the "minor" amendment included new issues which raised new deficiencies. These deficiencies were too numerous to be covered in a telephone amendment. See E-mails of 12/15,16/98 from Michael Smela.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 12/16/98

Endorsed by M.Smela

Page(s) 19

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Chemistry, #20 - #38, 12/18/98