CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-830

ADMINISTRATIVE

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:74-830 **Date of Submission: October 6, 1998 (original amendment date)**

Applicant's Name: Bausch & Lomb

Established Name: Desmopressin Acetate Nasal Solution, 0.01%

Labeling Deficiencies:

1. CONTAINER (5 mL)

   Satisfactory as of November 7, 1996

2. CARTON (5 mL)

   Satisfactory as of August 25, 1997

3. PHYSICIAN'S INSERT

   Due to changes in the labeling for the reference listed drug, please revise your insert labeling as follows and submit 12 copies of final printed physician insert and patient package insert labeling:

   a. TITLE

      We encourage the inclusion of "℞ only" in this section.

   b. DESCRIPTION

      i. Revise the first sentence of paragraph one to read as follows:

         Desmopressin Acetate Nasal Solution 0.01% is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation.

   c. PRECAUTIONS

      i. Information for Patients-Delete this subsection as it does not appear in the

approved labeling for the reference listed drug.

ii. Pregnancy Category B-

A. Revise the first paragraph of this subsection to read as follows:

Fertility studies have not been done. Teratology studies in rats and rabbits at doses from 0.05 to 10 μg/kg/day (approximately 0.1 times the maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to the fetus due to desmopressin acetate. There are, however no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

B. Delete the first sentence of paragraph two of this subsection:

There are no adequate and...

d. HOW SUPPLIED

i. Revise "Caution Federal law..." statement to read "℞ only".

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed insert labeling.

Please note that we reserve 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 annotated and explained.

Robert West
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 5 mL November 7, 1996

Carton Labeling: 5 mL August 25, 1997

Professional Package Insert Labeling: October 6, 1998

Patient Package Insert Labeling: October 6, 1998(Satisfactory in draft).

Revisions needed post-approval:

1. CONTAINER

   Revise "CAUTION: Federal law..." statement to read "℞ only".

2. CARTON

   Revise "CAUTION: Federal law..." statement to read "℞ only".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: DDAVP® Nasal Spray

NDA Number: 17-922

NDA Drug Name: Desmopressin Acetate Nasal Solution

NDA Firm: Rhone-Poulenc Rorer Pharmaceutical Corp.

Date of Approval of NDA Insert and supplement #: April 13, 1998 S-025

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: 17-922
Basis of Approval for the Carton Labeling: 17-922

Other Comments:

The innovator has received the following patents:

Patent #5500413, #5498598, #5482931, #5763407, and #5674850. We acknowledge your Paragraph IV certification and the innovator response for Patent #5674850. Please file certification for the remaining patents.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:74-830 **Date of Submission: October 6, 1998 (original amendment date)**

Applicant's Name: Bausch & Lomb

Established Name: Desmopressin Acetate Nasal Solution, 0.01%

Labeling Deficiencies:

1. CONTAINER (5 mL)

   Satisfactory as of November 7, 1996

2. CARTON (5 mL)

   Satisfactory as of August 25, 1997

3. PHYSICIAN'S INSERT

   Due to changes in the labeling for the reference listed drug, please revise your insert labeling as follows and submit 12 copies of final printed physician insert and patient package insert labeling:

   a. TITLE

      We encourage the inclusion of "℞ only" in this section.

   b. DESCRIPTION

      i. Revise the first sentence of paragraph one to read as follows:

         Desmopressin Acetate Nasal Solution 0.01% is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation.

   c. PRECAUTIONS

      i. Information for Patients-Delete this subsection as it does not appear in the

approved labeling for the reference listed drug.

ii. Pregnancy Category B-

A. Revise the first paragraph of this subsection to read as follows:

Fertility studies have not been done. Teratology studies in rats and rabbits at doses from 0.05 to 10 μg/kg/day (approximately 0.1 times the maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to the fetus due to desmopressin acetate. There are, however no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

B. Delete the first sentence of paragraph two of this subsection:

There are no adequate and...

d. HOW SUPPLIED

i. Revise "Caution Federal law..." statement to read "℞ only".

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed insert labeling.

Please note that we reserve 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 annotated and explained.

/S/

Robert West
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:74-830 **Date of Submission:** ~~**November 25, 1998**~~ December 1, 1998
(original amendment date)

Applicant's Name: Bausch & Lomb

Established Name: Desmopressin Acetate Nasal Solution, 0.01%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 5 mL November 7, 1996
Carton Labeling: 5 mL August 25, 1997
Professional Package Insert Labeling: Satisfactory as of ~~November 25,~~ December 1, 1998 submission.

Patient Package Insert Labeling: Satisfactory as of ~~November 25,~~ December 1, 1998 submission.

Revisions needed post-approval:
We acknowledge the firm's commitment to making these revisions as stated in their cover letter dated November 25, 1998.

1. CONTAINER

   Revise "CAUTION: Federal law..." statement to read "℞ only".

2. CARTON

   Revise "CAUTION: Federal law..." statement to read "℞ only".

3. PHYSICIAN'S INSERT

   a. TITLE

      We encourage the inclusion of "℞ only" in this section.

   b. HOW SUPPLIED

Revise "Caution Federal law..." statement to read "Rx only".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: DDAVP® Nasal Spray

NDA Number: 17-922

NDA Drug Name: Desmopressin Acetate Nasal Solution

NDA Firm: Rhone-Poulenc Rorer Pharmaceutical Corp.

Date of Approval of NDA Insert and supplement #: April 13, 1998 S-025

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: 17-922
Basis of Approval for the Carton Labeling: 17-922

Other Comments:

The innovator has received the following patents:

Patent #5500413, #5498598, #5482931, #5763407, and #5674850. We acknowledge your Paragraph IV certification and the innovator response for Patent #5674850. Please file certification for the remaining patents.

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Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
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If not USP, has the product name been proposed in the PF?		X	
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Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
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Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
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Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
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Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-830 Date of Submission: November 7, 1996

Applicant's Name: Bausch & Lomb Pharmaceuticals, Inc.

Established Name: Desmopressin Acetate Nasal Solution, 0.01%

Labeling Deficiencies:

1. CONTAINER (5 mL Bottle)

   Satisfactory

2. CARTON (5 mL Bottle)

   Satisfactory

3. INSERT

   Due to 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.

   b. CLINICAL PHARMACOLOGY

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

   c. WARNINGS

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

   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.

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.

iii. Nursing Mothers

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

e. ADVERSE REACTIONS

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

f. OVERDOSAGE

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

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.

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

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

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.

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 annotated and explained.

/S/

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