# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*
**ANDA 76-703**

***Name*:** Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), 10 mcg/0.1 mL

***Sponsor*:** Apotex Corp.

***Approval Date*:** January 27, 2005

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

## CONTENTS

| Reviews / Information Included in this Review | |
|---|---|
| Approval Letter | X |
| Tentative Approval Letter | X |
| Labeling | X |
| Labeling Reviews | X |
| Medical Review(s) | |
| Chemistry Reviews | X |
| Bioequivalence Reviews | X |
| Statistical Review(s) | |
| Microbiology Review(s) | |
| Administrative Documents | X |
| Correspondence | X |
| | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 76-703**

# APPROVAL LETTER

ANDA 76-703

JAN 27 2005

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: Apotex Inc.
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 26, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act(Act) for Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), 10 mcg/0.1 mL packaged in 5 mL bottles with a nasal pump dispenser.

Reference is also made to our Tentative Approval letter issued on November 30, 2004, and your amendments dated December 29, 2004, and January 24, 2005.

The listed drug product (RLD) referenced in your application, DDAVP Nasal Spray of Aventis Pharmaceutical Products Inc. (Aventis), is subject to periods of patent protection. The following U.S. patents for DDAVP Nasal Spray and their expiration dates are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

| U.S. Patent | Expiration Date |
|---|---|
| 5,482,931 (the '931 patent) | June 29, 2013 |
| 5,550,413 (the '413 patent) | June 29, 2013 |
| 5,674,850 (the '850 patent) | December 23, 2013 |
| 5,763,407 (the '407 patent) | June 29, 2013 |

As noted in your November 30, 2004, tentative approval letter, no legal action was brought against Apotex Inc. (Apotex) for infringement of the '413, '850, or '407 patents within the statutory 45 day period. However, litgation was brought Apotex in the United States District Court for the District of New

Jersey involving your challenge to the '931 patent (Ferring BV and Aventis Pharmaceuticals, Inc. v. Apotex Inc., Civil Action No. 03-3860 (MLC)(JJH). With respect to the '931 patent, you have informed the agency that Apotex has entered into a License Agreement with Ferring B.V. (Ferring) and Aventis Pharmaceuticals Inc. (Aventis) providing Apotex with a non-exclusive license to manufacture and commercialize Desmopressin Acetate Nasal Solution, 0.01% upon approval of this ANDA. In addition, documentation dated January 21, 2005 was submitted from counsel for Aventis and Ferring stating that they do not oppose the immediate final approval of this ANDA, thereby waiving any rights they might have to a 30-month stay of approval of this ANDA under section 505(j)(5)(B)(iii).

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Desmopressin Acetate Nasal Solution, 0.01%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (DDAVP Nasal Spray, 0.01%, of Aventis Pharmaceutical Products Inc.). This drug product is approved for storage at controlled room temperature.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend that you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20957

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 1/27/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-703
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

Electronic Labeling: \\CDSESUBOGD1\N76703\N_000\2004-08-27

Endorsements:
HFD-625/M.Smela M Smela* 1/26/05
HFD-625/A.Pendse 1/25/05
HFD-617/P.Chen 1/25/05
HFD-613/A.Payne
HFD-613/J.Grace
} See attached email

V:\FIRMSAM\Apotex\LTRS&REV\76703ap.doc

F/T by:

APPROVAL

*No CMC change since T/A on 11/30/04

11/26/04

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# TENTATIVE APPROVAL LETTER

ANDA 76-703

NOV 30 2004

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Marcy Macdonald
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 26, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), 10 mcg/0.1 mL packaged in 5 mL bottles with a nasal pump dispenser.

Reference is also made to your amendments August 19, 2003, and June 10, July 27, August 24, and August 27, 2004. We also acknowledge receipt of your correspondence dated May 11, and June 7, 2004, addressing the patent issues noted below.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the patent issue discussed below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, DDAVP Nasal Spray of Aventis Pharmaceutical Products Inc., is subject to periods of patent protection. The following patents

for DDAVP Nasal Spray and their expiration dates are currently listed in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

| U.S. Patent Number | Expiration Date |
|---|---|
| 5,482,931 (the '931 patent) | June 29, 2013 |
| 5,550,413 | June 29, 2013 |
| 5,674,850 | December 23, 2013 |
| 5,763,407 | June 29, 2013 |

Your ANDA contains paragraph IV patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray) under this ANDA. Section 505(j)(5)(B)(iii)[1] of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against Apotex Inc. (Apotex) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Apotex prior to the expiration of 45 days from the date the notices you provided under section 505(j)(2)(B)(i) were received by the NDA/patent holder(s). You have notified the Agency that Apotex complied with the requirements of section 505(j)(2)(B) of the Act. As a result, litigation was brought against Apotex in the United States District Court for the District of New Jersey involving a challenge to the '931 patent (Ferring BV and Aventis Pharmaceuticals, Inc. v. Apotex, Inc., Civil Action No. 03-3860).

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii), or such shorter or longer period as the court may have ordered, or,

[1] Because information on the '931 patent was submitted before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted. See MMA § 1101(c)(3).

b. the date the court decides[2] that the patent is invalid or not infringed. See section 505(j)(5)(B)(iii)(I), (II), and (III) of the Act.

c. the '931 patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Peter Chen, R.Ph., Project Manager, (301) 827-5848.

Sincerely yours,

Gary Buehler 11/30/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-703
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-625/A.Pendse/ 11/17/04

HFD-625/M.Smela/ 11/29/04

HFD-617/P.Chen/ 11/29/04

HFD-613/A.Payne 11/29/04

HFD-613/J.Grace/ 11/29/04

V:\FIRMSAM\Apotex\LTRS&REV\76703ta.doc 11/29/04 per telecon

F/T by 11/30/2004

TENTATIVE APPROVAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 76-703**

## LABELING

194 mm

50 mm

300 mm

PRESCRIBING INFORMATION

# Desmopressin Acetate Nasal Solution 0.01% (Nasal Spray)

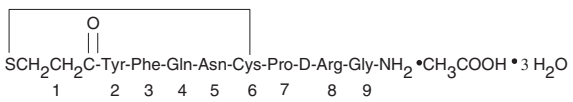
035701

**℞ Only**

Patient Instruction Sheet is attached.

## DESCRIPTION

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. The structural formula for the active ingredient is:




Mol. wt. 1183.34

Empirical formula: $C_{48}H_{74}N_{14}O_{17}S_2$

Chemical name: 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

Desmopressin acetate nasal solution is provided as an aqueous solution for intranasal use.

| Each mL contains: | |
|---|---|
| Desmopressin acetate | 0.1 mg |
| **Inactives:** | |
| Benzalkonium chloride solution (50% w/v) | 0.2 mg |
| Citric acid monohydrate | 1.7 mg |
| Sodium chloride | 7.5 mg |
| Sodium phosphate dibasic heptahydrate | 4.52 mg |
| Purified water to 1 mL | |

The desmopressin acetate nasal solution compression pump delivers 0.1 mL (10 µg) of desmopressin acetate per spray.

## CLINICAL PHARMACOLOGY

Desmopressin acetate nasal solution contains as active substance desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin. One mL (0.1 mg) of intranasal desmopressin acetate has an antidiuretic activity of about 400 IU; 10 µg of desmopressin acetate is equivalent to 40 IU.

1. The biphasic half-lives for intranasal desmopressin acetate were 7.8 and 75.5 minutes for the fast and slow phases, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone used in this condition. As a result, intranasal desmopressin acetate provides a prompt onset of antidiuretic action with a long duration after each administration.
2. The change in structure of arginine vasopressin to desmopressin acetate has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic doses are usually below threshold levels for effects on vascular or visceral smooth muscle.
3. Desmopressin acetate administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.

## INDICATIONS AND USAGE

**Primary Nocturnal Enuresis:**
Desmopressin acetate nasal solution is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other nonpharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

**Central Cranial Diabetes Insipidus:**
Desmopressin acetate nasal solution is indicated 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. It is ineffective for the treatment of nephrogenic diabetes insipidus.

The use of desmopressin acetate nasal solution in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal life-style with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to intranasal desmopressin acetate can be monitored by urine volume and osmolality.

Desmopressin acetate is also available as a solution for injection when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

## CONTRAINDICATIONS

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.

## WARNINGS

1. For intranasal use only.
2. When desmopressin acetate nasal solution is administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia with accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium and weight gain). Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

## PRECAUTIONS

**General:**
Intranasal desmopressin acetate at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Desmopressin acetate should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia. Rare severe allergic reactions have been reported with desmopressin acetate. Anaphylaxis has been reported with intravenous and intranasal administration of desmopressin acetate.

**Central Cranial Diabetes Insipidus:**
Since desmopressin acetate is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case intranasal desmopressin acetate should not be used. For such situations, desmopressin acetate injection should be considered.

**Primary Nocturnal Enuresis:**
If changes in the nasal mucosa have occurred, unreliable absorption may result. Desmopressin acetate nasal solution should be discontinued until the nasal problems resolve.

**Information for Patients:**
Patients should be informed that the desmopressin acetate nasal solution bottle accurately delivers 50 doses of 10 µg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 µg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

**Laboratory Tests:**
Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality measurements may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

**Drug Interactions:**
Although the pressor activity of desmopressin acetate is very low compared to the antidiuretic activity, use of large doses of intranasal desmopressin acetate with other pressor agents should only be done with careful patient monitoring.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**
Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

**Pregnancy:** *Teratogenic Effects Category B*
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.

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 fifteen year Swedish epidemiologic study of the use of desmopressin acetate in pregnant women with diabetes insipidus found the rate of birth

PHARMACIST - DETACH HERE AND GIVE LOWER PORTION TO PATIENT

PATIENT INSTRUCTION SHEET

# Desmopressin Acetate Nasal Solution 0.01% (Nasal Spray)

**℞ Only**

### A better way to deliver Desmopressin Acetate Nasal Solution
### Delivering Desmopressin Acetate Nasal Solution More Efficiently

Your doctor has prescribed Desmopressin Acetate Nasal Solution 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.

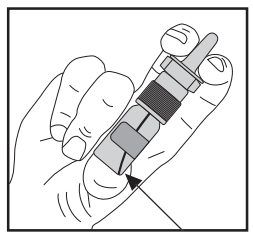
**NOTE:** In the event that the pharmacist has not assembled the spray pump, unscrew the white cap from the solution bottle and screw the spray pump tightly onto the bottle. Make sure the protective cap is on the spray pump.

**CAUTION:** The nasal spray pump accurately delivers 50 doses of 10 micrograms each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter per actuation may be substantially less than 10 micrograms of drug. Do not transfer any remaining solution to another bottle. Please read the following instructions carefully before using the spray pump.

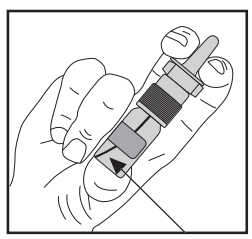
### Using Your Desmopressin Acetate Nasal Solution Pump

1. Remove protective cap.
2. **The spray pump must be primed prior to the first use.** To prime pump, press down 4 times.
3. Once primed, the spray pump delivers 10 micrograms of medication each time it is pressed.

To administer a 10-microgram dose, place the spray nozzle in nostril and press the spray pump once. If a higher dose has been prescribed, spray half the dose in each nostril. The spray pump cannot be used for doses less than 10 micrograms or doses other than multiples of 10 micrograms.



CORRECT



INCORRECT

**Desmopressin Acetate Nasal Solution 0.01% (US Product)**
**SAP Code:** 35701 RA Rev. 2 **Revision Date:** 08/23/04
**Reason for Revision:** Revise text for changes made to the reference listed drug
**Flat Size:** 194 mm x 300 mm **Finished Folded:** Size 194 mm x 50 mm
**Paper Stock:** 28 lb **Luminescence:** Yes

defects to be no greater than that in the general population; however, the statistical power of this study is low. 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.

**Nursing Mothers:**
There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable desmopressin acetate in breast milk following an intranasal dose of 10 µg. 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.

**Pediatric Use:** *Primary Nocturnal Enuresis*
Desmopressin acetate nasal solution has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) desmopressin acetate nasal solution administration has been shown to be safe and modestly effective in pediatric patients aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal desmopressin acetate in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

**Central Cranial Diabetes Insipidus:**
Desmopressin acetate nasal solution has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.

Since the spray cannot deliver less than 0.1 mL (10 µg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 µg) per dose.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

## ADVERSE REACTIONS

Infrequently, high dosages of intranasal desmopressin acetate have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percentage of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

| ADVERSE REACTION | PLACEBO (N=59) % | DESMOPRESSIN ACETATE 20 µg (N=60) % | DESMOPRESSIN ACETATE 40 µg (N=61) % |
|---|---|---|---|
| BODY AS A WHOLE | | | |
| Abdominal Pain | 0 | 2 | 2 |
| Asthenia | 0 | 0 | 2 |
| Chills | 0 | 0 | 2 |
| Headache | 0 | 2 | 5 |
| Throat Pain | 2 | 0 | 0 |
| NERVOUS SYSTEM | | | |
| Depression | 2 | 0 | 0 |
| Dizziness | 0 | 0 | 3 |
| RESPIRATORY SYSTEM | | | |
| Epistaxis | 2 | 3 | 0 |
| Nostril Pain | 0 | 2 | 0 |
| Respiratory Infection | 2 | 0 | 0 |
| Rhinitis | 2 | 8 | 3 |
| CARDIOVASCULAR SYSTEM | | | |
| Vasodilation | 2 | 0 | 0 |
| DIGESTIVE SYSTEM | | | |
| Gastrointestinal Disorder | 0 | 2 | 0 |
| Nausea | 0 | 0 | 2 |
| SKIN & APPENDAGES | | | |
| Leg Rash | 2 | 0 | 0 |
| Rash | 2 | 0 | 0 |
| SPECIAL SENSES | | | |
| Conjunctivitis | 0 | 2 | 0 |
| Edema Eyes | 0 | 2 | 0 |
| Lachrymation Disorder | 0 | 0 | 2 |

See WARNINGS for the possibility of water intoxication and hyponatremia.

## OVERDOSAGE

(See ADVERSE REACTIONS.) In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for desmopressin acetate or desmopressin acetate nasal solution.

An oral $LD_{50}$ has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

## DOSAGE AND ADMINISTRATION

**Primary Nocturnal Enuresis:**
Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 µg or 0.2 mL solution intranasally at bedtime. Adjustment up to 40 µg is suggested if the patient does not respond.

Some patients may respond to 10 µg and adjustment to that lower dose may be done if the patient has shown a response to 20 µg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with intranasal desmopressin acetate in primary nocturnal enuresis have not been conducted beyond 4-8 weeks.

**Central Cranial Diabetes Insipidus:**
Desmopressin acetate nasal solution dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to intranasal desmopressin acetate. The usual dosage range in adults is 0.1 to 0.4 mL daily, either as a single dose or divided into two or three doses. Most adults require 0.2 mL daily in two divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05 to 0.3 mL daily, either as a single dose or divided into two doses. About 1/4 to 1/3 of patients can be controlled by a single daily dose of desmopressin acetate administered intranasally.

The nasal spray pump can only deliver doses of 0.1 mL (10 µg) or multiples of 0.1 mL. If doses other than these are required, a rhinal tube delivery system may be used.

The spray pump must be primed prior to the first use. **To prime pump, press down four (4) times.** The bottle will now deliver 10 µg of drug per spray. Discard desmopressin acetate nasal solution (nasal spray) after 50 sprays since the amount delivered thereafter per spray may be substantially less than 10 µg of drug.

## INFORMATION FOR THE PHARMACIST

**Instruction For Assembly of Spray Pump:**
Assemble Desmopressin Acetate Nasal Solution 0.01% (Nasal Spray) prior to dispensing to the patient, according to the following instructions:

1. Open the carton and remove the spray pump and solution bottle.
2. Assemble the desmopressin acetate nasal solution by unscrewing the white cap from the solution bottle and screwing the spray pump tightly onto the bottle. Make sure the protective cap is on the spray pump.
3. Return desmopressin acetate nasal solution bottle to the carton for dispensing to the patient.

## HOW SUPPLIED

Desmopressin Acetate Nasal Solution is available in a 5 mL bottle with a nasal pump dispenser with dust cover and patient instruction sheet delivering 50 sprays of 10 µg (NDC 60505-0815-0).

**Store at 25°C (77°F) [see USP Controlled Room Temperature]; excursions permitted to 15 - 30°C (59 - 86°F). STORE BOTTLE IN UPRIGHT POSITION.**

Keep out of the reach of children.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL 33326

35701 August 2004

PHARMACIST - DETACH HERE AND GIVE LOWER PORTION TO PATIENT

4. Replace the protective cap on bottle after use. The pump will stay primed for up to one week. If the product has not been used for a period of one week, re-prime the pump by pressing once.
5. We have included a convenient check-off chart to assist you in keeping track of medication doses used. This will help assure that you receive 50 "full doses" of medication. Please note that the bottle has been filled with extra solution to accommodate the initial priming activity.

**Desmopressin Acetate Nasal Solution**
**50-Dose Check-off**

| | | | | |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| 6 | 7 | 8 | 9 | 10 |
| 11 | 12 | 13 | 14 | 15 |
| 16 | 17 | 18 | 19 | 20 |
| 21 | 22 | 23 | 24 | 25 |
| 26 | 27 | 28 | 29 | 30 |
| 31 | 32 | 33 | 34 | 35 |
| 36 | 37 | 38 | 39 | 40 |
| 41 | 42 | 43 | 44 | 45 |
| 46 | 47 | 48 | 49 | 50 |

1. Retain with medication or affix in convenient location.
2. Starting with dose #1, check off after each administration.
3. **Discard medication after 50 doses.**

**Store at 25°C (77°F) [see USP Controlled Room Temperature]; excursions permitted to 15 - 30°C (59 - 86°F). STORE BOTTLE IN UPRIGHT POSITION.**

Keep out of the reach of children.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

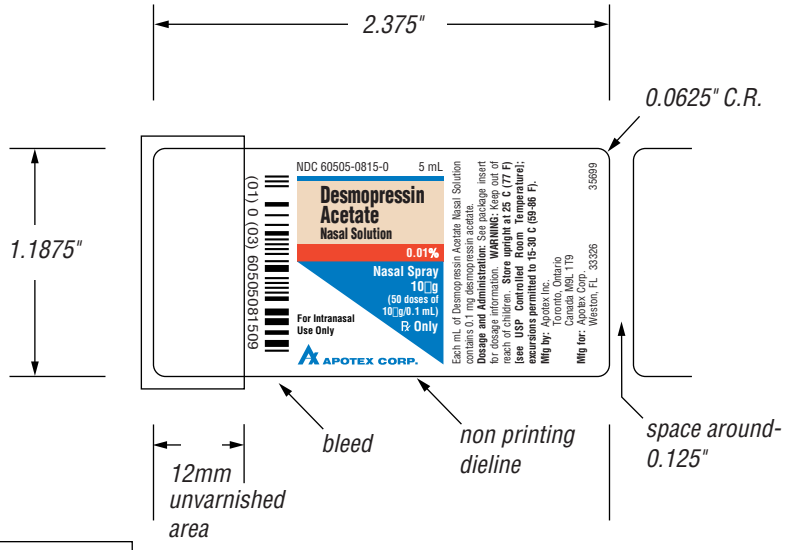
Manufactured for:
Apotex Corp.
Weston, FL 33326

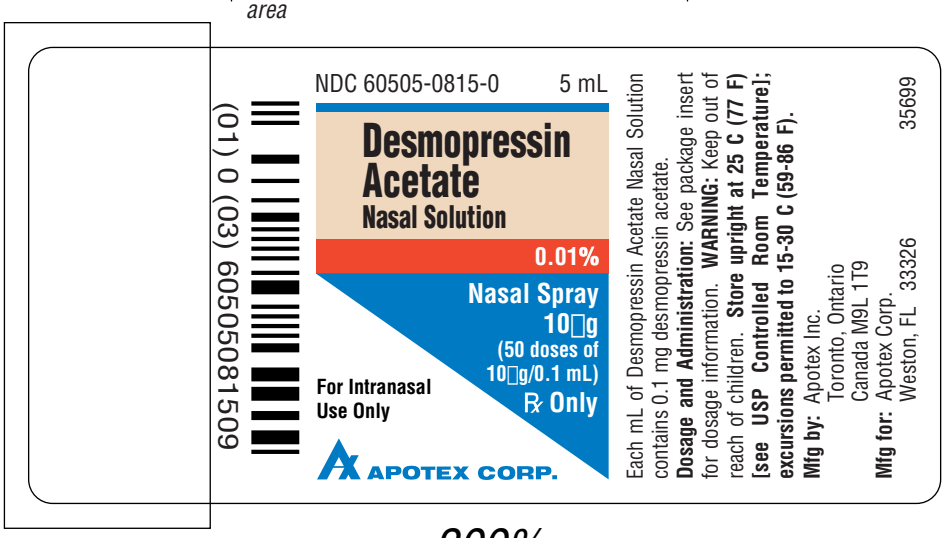
35701 August 2004

300 mm
50 mm
194 mm

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - **Richmond Hill Site** 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

| PRINTED PACKAGING MATERIAL PROOF | | | Copy of | Date Aug. 23, 2004 |
|---|---|---|---|---|
| Material Code 35699 | Product Name LBL DESMOPRESSIN ACETATE 0.01% NASAL SOL - 5ML | | | |
| Previous Code N/A | Label size 2.375" x 1.1875" (60.325 mm x 30.163 mm) | | | Change: Revise layout for printing capabilities, remove inactives, address, add RRS Limited barcode and revise text as per reference listed drug. |
| Colour (s) Black<br>Blue - 300C<br>Tan - 4675C<br>Red PMS 1788C<br>UV Varnish | Web Direction: Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. (PRINTING READS THIS WAY) | Printing Flexopress<br>Caliper 60# | Paper Stock Satin Litho<br>Adhesive Permanent | |
| Prepared by: | | Date: | | Reg. Affairs<br>Revision No.: 2 |




200%

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - **Richmond Hill Site** 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

| PRINTED PACKAGING MATERIAL PROOF | | | Copy of | Date August 23, 2004 |
|---|---|---|---|---|
| Material Code 35700 | Product Name CTN: DESMOPRESSIN ACET 0.01% NAS SOL - 5ML | | | |
| Previous Code N/A | Label size 4.724" x 2.362" x 1.358" (120 mm x 60 mm x 35 mm) Carton 1810E-3 | | | Change<br>Revised carton size, Location of lot & exp. and 128C Codes, address, revise upc code to ucc/ean code and revise text as per reference listed drug. |
| Colour (s) Black<br>Blue - 300C<br>Tan - 4675C<br>Red PMS 1788C<br>UV Varnish | | Printing Offset | Paper Stock N/A | |
| | | Caliper N/A | Adhesive N/A | |
| Prepared by: | | Date: | | Reg. Affairs<br>Revision No.: 2 |

035700

Unvarnished Area
(45 mm x 15 mm)
for placement of Lot No. & Expiry Date

NDC 60505-0815-0 5 mL

# Desmopressin Acetate
## Nasal Solution

**0.01%**

**Nasal Spray**
**10□g**
**(50 doses of 10□g/0.1 mL)**
**℞ Only**

**For Intranasal Use Only**

APOTEX CORP.

**Desmopressin Acetate Nasal Solution**
Each mL of Desmopressin Acetate Nasal Solution contains 0.1 mg desmopressin acetate. Inactives: 0.2 mg benzalkonium chloride solution (50% w/v), 1.7 mg citric acid monohydrate, 7.5 mg sodium chloride, 4.52 mg sodium phosphate dibasic heptahydrate and purified water to 1 mL.

**Dosage and Administration:** See package insert for dosage information. Before use, carefully read the accompanying instructions.

**WARNING:** Keep out of reach of children.

**Attention Pharmacist:**
See Prescribing Information for assembly instructions. Detach and dispense Patient Instructions attached to Package Insert.

**Store upright at 25 C (77 F) [see USP Controlled Room Temperature]; excursions permitted to 15-30 C (59-86 F).**

NDC 60505-0815-0 5 mL

# Desmopressin Acetate
## Nasal Solution

**0.01%**

**Nasal Spray**
**10□g**
**(50 doses of 10□g/0.1 mL)**
**℞ Only**

**For Intranasal Use Only**

APOTEX CORP.

**Mfg by:** Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

**Mfg for:** Apotex Corp.
Weston, FL 33326

(01) 1 (03) 6050508150 6

035700

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING#1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

FAX on 7/14/03

ANDA Number: 76-703 Date of Submission: March 26, 2003
Applicant's Name: Novex Pharma US agent is Apotex
Established Name: Desmopressin Acetate Nasal Solution 0.01% (Nasal Spray)

---

Labeling Deficiencies:

1. GENERAL COMMENT:

   We note the innovator storage temperature is at CRT 20-25 degrees Celsius. Revise your statement to read "Store upright at 25C (77F) [see USP Controlled Room temperature] excursion..." on all labels and labeling

2. CONTAINER (5mL) - Satisfactory. However, see General Comment.

3. CARTON : 1 X 5 mL

   a. Front panel - See comment under container.
   b. Side panel – Please qualify the inactive ingredients under a subsection heading titled "inactives".
   c. [redacted]

4. INSERT:

   a. TITLE - We encourage you to relocate "Rx Only" so that it appears below the product title. In addition state that "patient instruction sheet is attached".

   b. DESCRIPTION

      I. First sentence – add the strength of the product to the product name.
      II. [redacted] to read " The structural formula for the active ingredients is SCH..."
      III. The molecular formula should read "C48 H74N14O17S2".
      IV. Place "chemical name in front of 1-(3-mercap...
      V. Identify the inactive ingredients under a subsection heading "inactives".

   c. DOSAGE AND ADMINISTRATION, last paragraph

      I. "To prime pump, press down four (4) times" note minor change and phrase should appear in bold print.
      II. Last sentence – Insert "(Nasal Spray) just before "after 50 sprays".

   f. INFORMATION FOR THE PHARMACIST – Delete this section. It does not appear in the labeling of the innovator.

   g. HOW SUPPLIED

      I. See GENERAL COMMENT .
      II. "...with a nasal pump dispenser with dust cover and with patient instruction sheet".

5. PATIENT'S INSTRUCTIONS FOR USE - Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

| | |
|---|---|
| **ANDA Number** | 76-703 |
| **Date of Submission** | |
| **Applicant** | Novex Pharm |
| **Drug Name** | Desmopressin Acetate Nasal Solution |
| **Strength(s)** | 0.01% (Nasal Spray) |

| **FPL Approval Summary** | | |
|---|---|---|
| **Container Labels** | **XXXXXXXX** | **Submitted vol XX** |
| **Package Insert Labeling** | #XXXXRev. | **vol XX** |

**BASIS OF APPROVAL:**

**Patent Data For NDA 17-922**

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 5674850 | 12/23/13 | --- | | PIV | Same As |
| 5482931 | 6/29/13 | --- | | PIV | Same As |
| 5500413 | 6/29/13 | --- | | PIV | Same As |
| 5763407 | 6/29/13 | --- | | PIV | Same As |

**Exclusivity Data For NDA 17-922**

| Code/sup | Expiration | Description | Labeling impact |
|---|---|---|---|
| | | | |

| **Reference Listed Drug** | |
|---|---|
| RLD on the 356(h) form | DDAVP |
| NDA Number | 17-922/S-027 ( non-refrigerated product) |
| RLD established name | Desmopressin Acetate Nasal Solution o.o1% (Nasal Spray) |
| Firm | Phone-Poulenc Rorer Pharmaceuticals Inc. (Aventis Pharm Prod.-COMIS) |
| Currently approved PI | |
| AP Date | July 05. 2000 (non refrigerated product) |

Note.

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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | 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 1/2 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 | | |

**NOTES/QUESTIONS TO THE CHEMIST: The applicant propose a V shaped bottom. The RLD has a round shape bottom and the bottle needs to be titled so that the tubing draws from the deepest portion of the medication to ensure dosing accuracy. Is this the case with the applicant because they fail to put in instruction regarding tilting??**

---

FOR THE RECORD:

1. Review based on the labeling of DDAVP(NDA 17-922/S-027 (non refrigerated product) , Rhone-Poulenc Rorer ; approved July 15, 2000. Information regarding tilting the bottle has been excluded from this generic. Please note this same NDA# has a refrigerate product labeling that differs in Precaution Section and priming instruction from the non-refrigerated product.

2. Patent/ Exclusivities: Applicant filed a paragraph IV.

3. Storage Conditions:
   NDA – CRT 20-25C (see USP) Store bottle in upright position
   ANDA – RT 25C. Do not refrigerate. Store in upright position. Keep out of reach of children.
   USP – not a USP item

4. Dispensing Recommendations:
   NDA – dispense with patient instruction sheet
   ANDA – dispense with patient instruction sheet
   USP - NA

5. Scoring: NA
   NDA -
   ANDA -
   USP -

6. Product Line:
   The innovator markets their product in 5 mL amber round bottom bottle with safety cap
   The applicant proposes to market their product in 5 mL v shaped amber glass bottom bottle with safety cap. Page 759 vol. 1.2 manufactured by Novex for apotex. ——is used as an outside testing facility

7. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to

be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 491 (Volume 1.1) application uses 4.52 mg of Sodium phosphate dibasic heptahydrate were as the RLD uses 3 mg of disodium phosphate dihydrate

8. Minor differences in RLD and applicant are based on our approved generic ANDA 74-830 (Bausch & Lomb the refrigerated product) pictures should be provided by this applicant.

---

**Date of Review: June 30, 2003** **Date of Submission: March 26, 2003**

---

cc: ANDA: 76-703
DUP/DIVISION FILE
HFD-613/APayne/Jgrace (no cc)
V:firmsnz/novex/lets&rev/76703na1.lab
Review

7/2/03
7/11/2003

APPEARS THIS WAY
ON ORIGINAL

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

| | |
|---|---|
| **ANDA Number** | 76-703 |
| **Date of Submission** | August 19, 2003 |
| **Applicant** | Novex Pharm |
| **Drug Name** | Desmopressin Acetate Nasal Solution |
| **Strength(s)** | 0.01% (Nasal Spray) |

| FPL Approval Summary | | |
|---|---|---|
| **Container Labels** | | **Submitted** |
| 10 mcg | 5 mL | Aug 19, 2003 vol 2.1 blue |
| **Carton Labeling** | 1 X 5 mL | Aug 19, 2003 vol 2.1 blue |
| **Package Insert Labeling** | #35701Rev. 8/2003 | Aug 19, 2003 vol 2.1 blue |
| **Patient information sheet** | attached | Aug 19, 2003 vol 2.1 blue |

BASIS OF APPROVAL:

**Patent Data For NDA 17-922**

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 5674850 | 12/23/13 | --- | Process: High purity desmopressin produced in large single batches | PIV | No impact |
| 5482931 | 6/29/13 | --- | Stabilized pharmaceutical peptide compositions | PIV | Same as |
| 5500413 | 6/29/13 | --- | Process for manufacture of 1-deamino-8-D-arginine vasopressin | PIV | No impact |
| 5763407 | 6/29/13 | --- | Process: High-purity desmopressin produced in large single batches | PIV | No impact |

**Exclusivity Data For NDA 17-922**

| Code/sup | Expiration | Description | Labeling impact |
|---|---|---|---|
| none | | | none |

| **Reference Listed Drug** | |
|---|---|
| RLD on the 356(h) form | DDAVP |
| NDA Number | 17-922/S-027 ( non-refrigerated product) |
| RLD established name | Desmopressin Acetate Nasal Solution o.o1% (Nasal Spray) |
| Firm | Phone-Poulenc Rorer Pharmaceuticals Inc. (Aventis Pharm Prod.-COMIS) |

Currently approved PI S-027
AP Date July 05. 2000 (non refrigerated product)

Note. Encourage to add "————————————————" to main panel of the carton and container. Add a "————————————" and changed "empirical" to "————" in the description sections. S-025 pending. The generic product must be assembled before use

**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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | 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 1/2 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 | | |

**NOTES/QUESTIONS TO THE CHEMIST/Microbiologist:**

1.The generic applicant proposed product **must be assemble**, where as, the reference listed drug product is an assembled product. Does the generic "must be assemble" product pose a risk of a less sterile product and possible contamination? The instructions add a note to the pharmacist/patient to assemble the product. It does not metnion in a sterile environment. The RLD product instruction is not an issue because the product is already assemble. The DP is not sterile to start with.

2.The applicant propose a V shaped bottom. The RLD has a round shape bottom and the bottle needs to be tilted so that the tubing draws from the deepest portion of the medication to ensure dosing accuracy. Is this the case with the generic applicant because they fail to put in instruction regarding tilting??

Tilting instruction not needed. See response on page 6 of 12/23/03 amendment.

**FOR THE RECORD:**

M Shuler 2/4/04

1. Review based on the labeling of DDAVP(NDA 17-922/S-027 (non refrigerated product) , Rhone-Poulenc Rorer ; approved July 15, 2000. Information regarding tilting the bottle has been excluded from this generic. Please note this same NDA# has a refrigerate product labeling that differs in Precaution Section and priming instruction from the non-refrigerated product. The RLD used the "ug" unit. We will allow our generic to retain "ug" rather than change to "mcg"

2. Patent/ Exclusivities: Applicant filed a paragraph IV.

3. Storage Conditions:
   NDA – CRT 20-25C (see USP) Store bottle in upright position
   ANDA – RT 25C. Do not refrigerate. Store in upright position. Keep out of reach of children.
   USP – not a USP item

4. Dispensing Recommendations:
   NDA – dispense with patient instruction sheet
   ANDA – dispense with patient instruction sheet
   USP - NA

5. Scoring: NA

NDA -
ANDA -
USP -

6. Product Line:
The innovator markets their product in 5 mL amber round bottom bottle with safety cap
The applicant proposes to market their product in 5 mL v shaped amber glass bottom bottle with safety cap. Page 759 vol. 1.2 manufactured by Novex for apotex. [redacted] is used as an outside testing facility

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 491 (Volume 1.1) application uses 4.52 mg of Sodium phosphate dibasic heptahydrate were as the RLD uses 3 mg of disodium phosphate dihydrate.

8. The RLD has an assembled product, where as this generic has a "must be assembled" by the pharmacist" product. My concerns where that the products sterility my be compromised and that the patient would have to assemble the product, if the Pharmacist fell to read the box. I conferred with John in that should the products (RLD and generic) have the same assemble requirement. John, said that the "must be assemble" product should be ok. The bottle must be uncapped and then the nasal component attached to the bottle. The tip of the nasal spray has a protective cap on it. Other editoral minor differences in RLD and applicant are based on our approved generic ANDA 74-830 (Bausch & Lomb the refrigerated product) pictures should be provided by this applicant.

---

**Date of Review: October 27, 2003** **Date of Submission: August 19, 2003**

---

cc: ANDA: 76-703
DUP/DIVISION FILE
HFD-613/APayne/Jgrace (no cc)
V:firmsnz/novex/lets&rev/76703ap.lab
Review

Jgrace 10/27/03
JohnGm 10/31/03

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

| | |
|---|---|
| **ANDA Number** | 76-703 |
| **Date of Submission** | August 27, 2004 |
| **Applicant** | Novex Pharm |
| **Drug Name** | Desmopressin Acetate Nasal Solution |
| **Strength(s)** | 0.01% (Nasal Spray), 10 mcg/0.1 mL/Spray, 5 mL |

| **FPL Approval Summary** | | |
|---|---|---|
| **Container Labels** | | **Submitted FPL- EDR** |
| 10 mcg | 5 mL | \\CDSESUBOGD1\N76703\N_000\2004-08-27 |
| **Carton Labeling** | 1 X 5 mL | \\CDSESUBOGD1\N76703\N_000\2004-08-27 |
| **Package Insert Labeling** | #35701Rev. 8/2004 | \\CDSESUBOGD1\N76703\N_000\2004-08-27 |
| **Patient information sheet** | attached | \\CDSESUBOGD1\N76703\N_000\2004-08-27 |

**BASIS OF APPROVAL:**

**Patent Data For NDA 17-922**

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 5674850 | 12/23/13 | --- | Process: High purity Desmopressin produced in large single batches | PIV | No impact |
| 5482931 | 6/29/13 | --- | Stabilized pharmaceutical peptide compositions | PIV | Same as |
| 5500413 | 6/29/13 | --- | Process for manufacture of 1-deamino-8-D-arginine vasopressin | PIV | No impact |
| 5763407 | 6/29/13 | --- | Process: High-purity Desmopressin produced in large single batches | PIV | No impact |

**Exclusivity Data For NDA 17-922**

| Code/sup | Expiration | Description | Labeling impact |
|---|---|---|---|
| none | | | none |

**Reference Listed Drug**

| | |
|---|---|
| RLD on the 356(h) form | DDAVP |
| NDA Number | 17-922/S-027 ( non-refrigerated product) |
| RLD established name | Desmopressin Acetate Nasal Solution o.o1% (Nasal Spray) |
| Firm | Phone-Poulenc Rorer Pharmaceuticals Inc. (Aventis Pharm Prod.-COMIS) |
| Currently approved PI | S-031 |
| AP Date | Nov. 12, 2003 (non refrigerated product) |

Note. Encourage to add "[redacted]" to main panel of the carton and container. Add a "[redacted]" and changed "empirical" to "[redacted]" in the description

**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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | 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 1/2 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 | | |

**NOTES/QUESTIONS TO THE CHEMIST/Microbiologist:**

1.The generic applicant proposed product **must be assemble**, where as, the reference listed drug product is an assembled product. Does the generic "must be assembled" product pose a risk of a less sterile product and possible contamination? The instruction adds a note to the pharmacist/patient to assemble the product. It does not mention to assemble in a sterile environment. The RLD product instruction is not an issue because the product is already assembled. *

2.The applicant propose a V shaped bottom. The RLD has a round shape bottom and the bottle needs to be tilted so that the tubing draws from the deepest portion of the medication to ensure dosing accuracy. Is this the case with the generic applicant because they fail to put in instruction regarding tilting?? *

---

**FOR THE RECORD:** * Answered in previous cycle.

1. Review based on the labeling of DDAVP(NDA 17-922/S-027 (non refrigerated product) , Rhone-Poulenc Rorer ; approved July 15, 2000. Information regarding tilting the bottle has been excluded from this generic. Please note this same NDA# has a refrigerate product labeling that differs in the Precaution Section and priming instruction from the non-refrigerated product. The RLD used the "ug" unit. We will allow our generic to retain "ug" rather than change to "mcg". The refrigerated product is a 2.5 mL rhinal tube nasal solution. The non-refrigerated product is a 5 mL Nasal Spray (metered according to orange book). The generic uses the established name Desmopressin acetate Nasal Solution 0.01% (Nasal Spray). The non refrigerated is a 0.01 mg/Spray or 10 mcg/0.1 mL/spray

2. Patent/ Exclusivities: Applicant filed a paragraph IV.

3. Storage Conditions:
   NDA – CRT 20-25C (see USP) Store bottle in upright position
   ANDA – RT 25C. Do not refrigerate. Store in upright position. Keep out of reach of children.
   USP – not a USP item

4. Dispensing Recommendations:
   NDA – dispense with patient instruction sheet
   ANDA – dispense with patient instruction sheet
   USP - NA

5. Scoring: NA
   NDA -
   ANDA -
   USP -

NDA -
ANDA -
USP -

6. Product Line:
The innovator markets their product in 5 mL amber round bottom bottle with safety cap
The applicant proposes to market their product in 5 mL v shaped amber glass bottom bottle with safety cap. Page 759 vol. 1.2 manufactured by Novex for apotex. — is used as an outside testing facility

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 491 (Volume 1.1) application uses 4.52 mg of Sodium phosphate dibasic heptahydrate were as the RLD uses 3 mg of Disodium phosphate dihydrate.

8. The RLD has an assembled product, where as this generic has a "must be assembled" by the pharmacist" product. My concerns were that the products sterility may be compromised and that the patient would have to assemble the product, if the Pharmacist fails to read the box. I conferred with John in that should the products (RLD and generic) have the same assemble requirement. John said that the "must be assembled" product should be ok. The bottle must be uncapped and then the nasal component attached to the bottle. The tip of the nasal spray has a protective cap on it. Other editorial minor differences in RLD and applicant are based on our approved generic ANDA 74-830 (Bausch & Lomb the refrigerated product) pictures should be provided by this applicant.

---

**Date of Review: 9/14/04** **Date of Submission: August 27, 2004**

---

cc: ANDA: 76-703
DUP/DIVISION FILE
HFD-613/APayne/Jgrace (no cc)
V:firmsnz/novex/lets&rev/76703ap2.lab
Review
**FPL- EDR: \\CDSESUBOGD1\N76703\N_000\2004-08-27**

9/21/04
9/14/04

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# CHEMISTRY REVIEWS

#1

# ANDA 76-703

## Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

**Novex Pharma**

**Anil D. Pendse**

**Division of Chemistry 1**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-703

2. REVIEW #: 1

3. REVIEW DATE: 9/11/03

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| None | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original submission | 3/26/03 |
| New Correspondence | 5/29/03 |
| Patent amendment | 7/3/03 |
| Patent amendment | 8/25/03 |

7. NAME & ADDRESS OF APPLICANT:

Name: Novex Pharma

Address: 380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Executive Summary Section

Representative: Marcy MacDonald
Apotex Corporation
51 Lakeview Parkway, Suite 127
Vernon Hills, Ill 60061

Telephone: (847) 573-9999

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Desmopressin Acetate Nasal Solution , 0.01%

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed Drug DDAVP® Nasal Spray, Desmopressin Acetate, 0.01%., NDA 17922 held by Aventis.

10. PHARMACOL. CATEGORY: Nocturnal Enuresis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 µg/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

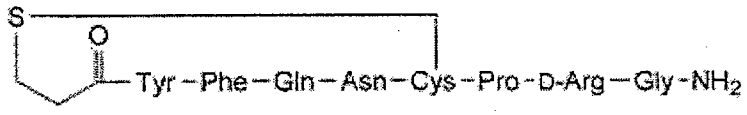
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-Mercaptopropionyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagyl-L-cysteinyl-L-propyl-D-arginyl-glycinamide disulfide acetate (salt) hydrate




$C_{46}H_{64}N_{14}O_{12}S_2$ 1069 *16679-58-6*

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Inadequate | 7/28/03 | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | | |
| Methods Validation | Will be requested later | | |
| Labeling | Deficient | 7/11/03 | Payne/Grace |
| Bioequivalence | Pending | | |
| EA | Acceptable | 9/11/03 | A. Pendse |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

**Note:** This ANDA was assigned in error by the acting team leader as it should have been held for expertise (i.e. peptide, metered dosage). The Division Director decided that the review should be completed with Team Leader oversight as significant effort was expended prior to the error being noticed. MS 9/22/03

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-703

## *The Executive Summary*

## I. Recommendations

**A. Recommendation and Conclusion on Approvability**
Not approvable (NA) Minor

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
None identified at this time

## II. Summary of Chemistry Assessments

**A. Description of the Drug Product(s) and Drug Substance(s)**
Drug Product is Desmopressin Acetate Nasal Solution , 0.01% and it is non-USP product

Drug substance Desmopressin Acetate is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

**B. Description of How the Drug Product is Intended to be Used**
Desmopressin Acetate has been used for many years for treatment of patients with primary nocturnal enuresis and central carnial diabetes insipidus and historically has been found to be safe and efficacious. It is used as nasal spray.

**C. Basis for Approvability or Not-Approval Recommendation**
Specifications provided for drug substance, drug product and stability are inadequate.

## III. Administrative

**A. Reviewer's Signature**
Anil D. Pendse

9/17/03

**B. Endorsement Block**

Chemist/APendse/9/11/03
ChemistryTeamLeader/MSmela/9/11/03
ProjectManager/PChen//9/11/03

**C. CC Block**

APPEARS THIS WAY
ON ORIGINAL

Redacted 25 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

5. Your response must also address the labeling deficiencies.

Sincerely yours,

M Smela for 9/22/03

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

cc: ANDA 76-703
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/9/11/03 9/17/03

HFD-625/MSmela/Team leader/ 9/12/03 9/22/03

HFD-617/PChen/Project manager/ 9/12/03 9/22/03

F/T by/ard/9/15/03

V:\FIRMSNZ\NOVEX\LTRS&REV\76703 CR 1.doc
**TYPE OF LETTER:** NOT APPROVABLE -MINOR

APPEARS THIS WAY
ON ORIGINAL

#2

# ANDA 76-703

## Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

**Novex Pharma**

**Anil D. Pendse**

**Division of Chemistry 1**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-703

2. REVIEW #: 2

3. REVIEW DATE: 2/5/04

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original submission | 3/26/03 |
| New Correspondence | 5/29/03 |
| Patent amendment | 7/3/03 |
| Patent amendment | 8/25/03 |
| Labeling amendment | 8/19/03 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Minor amendment | 12/23/03 |

7. NAME & ADDRESS OF APPLICANT:

Name: Novex Pharma

Address: 380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Executive Summary Section

Representative: Marcy MacDonald
Apotex Corporation
616 Heathrow Drive
Lincolnshire, Ill 60069

Telephone: (847) 521-8005

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Desmopressin Acetate Nasal Solution , 0.01%

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed Drug DDAVP® Nasal Spray, Desmopressin Acetate, 0.01%., NDA 17922 held by Aventis.

10. PHARMACOL. CATEGORY: Nocturnal Enuresis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 µg/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

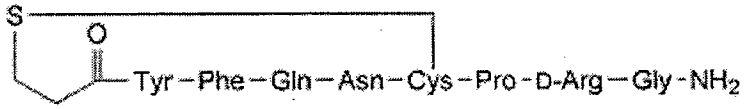
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-Mercaptopropionyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagyl-L-cysteinyl-L-propyl-D-arginyl-glycinamide disulfide acetate (salt) hydrate




$C_{46}H_{64}N_{14}O_{12}S_2$ 1069 *16679-58-6*

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | 1/28/04 | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 1/7/04 | S. Adams |
| Methods Validation | Issued this cycle. | | |
| Labeling | Acceptable | 10/27/03 | Payne/Grace |
| Bioequivalence | Pending | | |
| EA | Acceptable | 9/11/03 | A. Pendse |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __x__ No If no, explain reason(s) below:

Minor Amendmentd

**Note:** This ANDA was originally assigned in error by the acting team leader as it should have been held for expertise (i.e. peptide, metered dosage). The Division Director decided that the review should be completed with Team Leader oversight as significant effort was expended prior to the error being noticed.

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-703

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not approvable (NA) Minor

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Drug product is Desmopressin Acetate Nasal Solution , 0.01% and it is non-USP product

Drug substance Desmopressin Acetate is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

### B. Description of How the Drug Product is Intended to be Used

Desmopressin Acetate has been used for many years for treatment of patients with primary nocturnal enuresis and central carnial diabetes insipidus and historically has been found to be safe and efficacious. It is used as nasal spray.

### C. Basis for Approvability or Not-Approval Recommendation

Specifications provided for drug product and stability are not justified.

## III. Administrative

Executive Summary Section

**A. Reviewer's Signature**
Anil D. Pendse

**B. Endorsement Block**

Chemist/APendse/2/6/04
ChemistryTeamLeader/MSmela/2/6/04
ProjectManager/PChen//2/6/04

**C. CC Block**

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

Weights.

33. **ESTABLISHMENT INSPECTION :** Acceptable on 2/4/04 by S. Adams

34. **BIOEQUIVALENCE :** Pending Review

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION**: Firm has requested categorical exclusion per 21 CFR 25.24 (c) (1) 4

Firm acknowledges the following comments.

1. **Bioequivalence information is pending review and will be communicated to them directly.**

2. **An acceptable compliance evaluation is needed for the approval of their ANDA application.**

3. **A satisfactory Methods Validation study is needed to support the ANDA. Samples will be forwarded upon request.**

4. **Please provide any additional stability data that is available.**
   Response
   As requested, an updated stability report for Batch No. 2X130 with 12 months shelf life data and Batch No. 8X450 with 36 months data has been provided in Attachment No. 15.
   Data meet the requirements.

4. **Your response must also address the labeling deficiencies.**
   Response
   Firm received a labeling deficiency letter from the Agency on July 14, 2003 and provided a response on August 8, 2003.

APPEARS THIS WAY
ON ORIGINAL

## 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-703 APPLICANT: Novex Pharma

DRUG PRODUCT: Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your Bioequivalence information is pending review.

2 We have scheduled the Method Validation study. Please provide samples promptly when contacted.

Sincerely yours,

M Smela for 2/13/04

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-703
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/2/6/04 2/11/04

HFD-625/MSmela/Team leader/2/6/04 2/13/04

HFD-617/PChen/Project manager/2/6/04 2/13/04

F/T by: ard/2/9/04

V:\FIRMSNZ\NOVEX\LTRS&REV\76703 CR 2.doc
**TYPE OF LETTER:** NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

#3

# ANDA 76-703

## Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

**Novex Pharma**

**Anil D. Pendse**

**Division of Chemistry 1**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-703

2. REVIEW #: 3

3. REVIEW DATE: 7/9/04

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original submission | 3/26/03 |
| New Correspondence | 5/29/03 |
| Patent amendment | 7/3/03 |
| Patent amendment | 8/25/03 |
| Labeling amendment | 8/19/03 |
| Minor amendment | 12/23/03 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed* | Document Date |
|---|---|
| Patent amendment | 5/11/04 |
| *Minor amendment | 5/20/04 |
| Patent amendment request for additional information | 6/07/04 |
| New correspondence about name change to Apotex Inc. | 6/10/04 |

7. NAME & ADDRESS OF APPLICANT:

## CHEMISTRY REVIEW

Executive Summary Section

| | |
|---|---|
| Name: | Novex Pharma |
| Address: | 380 Elgin Mills Road East<br>Richmond Hill, Ontario<br>Canada L4C 5H2 |
| Representative: | Marcy MacDonald<br>Apotex Corporation<br>616 Heathrow Drive<br>Lincolnshire, Ill 60069 |
| Telephone: | (847) 521-8005 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Desmopressin Acetate Nasal Solution , 0.01%

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug DDAVP® Nasal Spray, Desmopressin Acetate, 0.01%., NDA 17922 held by Aventis.

10. PHARMACOL. CATEGORY: Nocturnal Enuresis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 µg/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

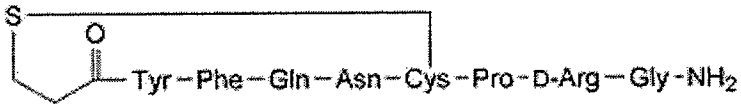
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x___Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-Mercaptopropionyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagyl-L-cysteinyl-L-propyl-D-arginyl-glycinamide disulfide acetate (salt) hydrate




$C_{46}H_{64}N_{14}O_{12}S_2$ 1069 *16679-58-6*

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | 7/7/04 | CTD Format |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 2/4/04 | S. Adams |
| Methods Validation | Acceptable | 6/2/04 | NERL |
| Labeling | Acceptable | 10/27/03 | Payne/Grace |
| Bioequivalence | Deficient | 6/4/04 | |
| EA | Acceptable | 9/11/03 | A. Pendse |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __x__ No If no, explain reason(s) below:

Minor Amendment

**Note:** This ANDA was originally assigned in error by the acting team leader as it should have been held for expertise (i.e. peptide, metered dosage). The Division Director decided that the review should be completed with Team Leader oversight as significant effort was expended prior to the error being noticed.

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-703

## *The Executive Summary*

## I. Recommendations

**A. Recommendation and Conclusion on Approvability**
Not Approvable (NA) Minor.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
None identified at this time

## II. Summary of Chemistry Assessments

**A. Description of the Drug Product(s) and Drug Substance(s)**
Drug product is Desmopressin Acetate Nasal Solution , 0.01% and it is non-USP product

Drug substance Desmopressin Acetate is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

**B. Description of How the Drug Product is Intended to be Used**
Desmopressin Acetate has been used for many years for treatment of patients with primary nocturnal enuresis and central carnial diabetes insipidus and historically has been found to be safe and efficacious. It is used as nasal spray.

**C. Basis for Approvability or Not-Approval Recommendation**
This application is not approvable due to issues with drug product release & stability limits and bioequivalence.

## III. Administrative

**A. Reviewer's Signature**
Anil D. Pendse 7/21/04
**B. Endorsement Block** 7/21/04
Review Chemist/APendse/7/16/04

Chemistry TeamLeader/MSmela/7/16/04

Project Manager/PChen/7/9/04
**C. CC Block**

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

33. **ESTABLISHMENT INSPECTION :** Acceptable on 2/4/04 by S. Adams

34. **BIOEQUIVALENCE** : Not Acceptable
The Bioequivalence has completed the review of firm's application, deficiencies have been identified and communicated to the firm on 6/4/04.

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION**: Firm has requested categorical exclusion per 21 CFR 25.24 (c) (1) 4 which can be granted.

## 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-703 APPLICANT: Novex Pharma

DRUG PRODUCT: Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]

2. Bioequivalence has not been established. Please reply to the bioequivalence deficiency letter sent to you by facsimile on June 4, 2004.

Sincerely yours,

M Smilan for 7/26/04

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

cc: ANDA 76-703
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/7/16/04 7/21/04

HFD-625/MSmela/Team leader/7/16/04 M Smela 7/26/04

HFD-617/PChen/Project manager/7/16/04 7/26/04

F/T by: ard/7/20/04

V:\FIRMSNZ\NOVEX\LTRS&REV\76703 CR 3.doc

**TYPE OF LETTER:** NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

#4

# ANDA 76-703

## Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray)

**Novex Pharma**

**Anil D. Pendse**

**Division of Chemistry 1**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-703

2. REVIEW #: 4

3. REVIEW DATE: 11/1/04

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original submission | 3/26/03 |
| New Correspondence | 5/29/03 |
| Patent amendment | 7/3/03 |
| Patent amendment | 8/25/03 |
| Labeling amendment | 8/19/03 |
| Patent amendment | 5/11/04 |
| Minor amendment | 5/20/04 |
| Patent amendment request for additional information | 6/07/04 |
| New correspondence about name change to Apotex Inc. | 6/10/04 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed* | Document Date |
|---|---|
| Bioequivalency amendment | 7/8/04 |
| Gratuitous Amendment | 7/27/04 |
| Bioequivalency amendment (request to withdraw) | 7/29/04 |
| Bioequivalency amendment | 8/4/04 |
| *Minor amendment | 8/24/04 |
| Labeling amendment | 8/27/04 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Apotex Inc. |
| Address: | 380 Elgin Mills Road East<br>Richmond Hill, Ontario<br>Canada L4C 5H2 |
| Representative: | Marcy MacDonald<br>Apotex Corporation<br>616 Heathrow Drive<br>Lincolnshire, Ill 60069 |
| Telephone: | (847) 521-8005 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Desmopressin Acetate Nasal Solution , 0.01%

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed Drug DDAVP® Nasal Spray, Desmopressin Acetate, 0.01%., NDA 17922 held by Aventis.

10. PHARMACOL. CATEGORY: Nocturnal Enuresis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 µg/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

Executive Summary Section

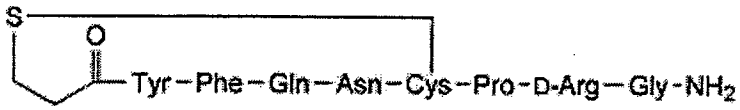
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-Mercaptopropionyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagyl-L-cysteinyl-L-propyl-D-arginyl-glycinamide disulfide acetate (salt) hydrate




$C_{46}H_{64}N_{14}O_{12}S_2$ 1069 *16679-58-6*

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 3 | Adequate | 7/7/04 | CTD Format |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: None**

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 2/4/04 | S. Adams |
| Methods Validation | Acceptable | 6/2/04 | NERL |
| Labeling | Acceptable | 9/21/04 | Payne/Grace |
| Bioequivalence | Acceptable | 11/6/04 | Osterhout/Nerurkar |
| EA | Acceptable | 9/11/03 | A. Pendse |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __x__ No If no, explain reason(s) below:
Minor Amendment
**Note:** This ANDA was originally assigned in error by the acting team leader as it should have been held for expertise (i.e. peptide, metered dosage). The Division Director decided that the review should be completed with Team Leader oversight as significant effort was expended prior to the error being noticed.

# The Chemistry Review for ANDA 76-703

## *The Executive Summary*

## I. Recommendations

**A. Recommendation and Conclusion on Approvability**
Application is approvable

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
None identified at this time

## II. Summary of Chemistry Assessments

**A. Description of the Drug Product(s) and Drug Substance(s)**
Drug product is Desmopressin Acetate Nasal Solution , 0.01% and it is non-USP product

Drug substance Desmopressin Acetate is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

**B. Description of How the Drug Product is Intended to be Used**
Desmopressin Acetate has been used for many years for treatment of patients with primary nocturnal enuresis and central carnial diabetes insipidus and historically has been found to be safe and efficacious. It is used as nasal spray.

**C. Basis for Approvability or Not-Approval Recommendation**
All the deficiencies have been answered satisfactorily. DMF remains adequate. Labeling, Bioequivalence, EER and Method Validation are acceptable.

## III. Administrative

**A. Reviewer's Signature**
Anil D. Pendse
11/1/04

11/17/04

**B. Endorsement Block**

Review Chemist/APendse/11/10/04 11/17/04

Chemistry TeamLeader/MSmela/11/10/04 11/29/04

Project Manager/PChen/11/1/04

**C. CC Block**

APPEARS THIS WAY
ON ORIGINAL

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

cc: ANDA 76-703
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/11/10//04

HFD-625/MSmela/Team leader/11/10//04

F/T by: ard/11/15/04
V:\FIRMSNZ\NOVEX\LTRS&REV\76703 CR 4.doc

**TYPE OF LETTER:** Approvable

APPEARS THIS WAY
ON ORIGINAL

**Final Approval Following a Tentative Approval**
**Abbreviated New Drug Application Regulatory Assessment**

---

1. ANDA # 76-703

2. NAME AND ADDRESS OF APPLICANT
   Apotex Inc.
   380 Elgin Mills Road East
   Richmond Hills, Ontario
   Canada L4C 5H2

3. LEGAL BASIS FOR SUBMISSION
   505(j)
   RLD: DDAVP Nasal Spray of Aventis Pharmaceutical Products Inc.
   NDA:17-922

4. PROPRIETARY NAME
   none

5. NONPROPRIETARY NAME
   Desmopressin Acetate Nasal Solution, 0.01%

6. CURRENT SUBMISSIONS AND OTHER DATES:

| | |
|---|---|
| TA Letter | 11/30/2004 |
| Minor Amendment | 12/29/2004 |

7. PHARMACOLOGICAL CATEGORY
   Synthetic analogue of natural hormone arginine vasopressin. Indicated for Primary Nocturnal Enuresis and Central Cranial Diabetes Insipidus.

8. Rx or OTC
   Rx

9. SAMPLES AND RESULTS
   Acceptable on 6/2/04

10. LABELING STATUS
    Acceptable on 9/21/04

11. BIOEQUIVALENCY STATUS
    Acceptable on 11/6/04

12. MICROBIOLOGY STATUS
    N.A.

13. ESTABLISHMENT INSPECTION
    Acceptable on 2/4/04

14. CONCLUSIONS AND RECOMMENDATIONS

Ready for full approval. No CMC changes reported. It is Office policy not to check DMFs for new submissions when bringing an ANDA from tentative to full approval.

| PROJECT MANAGER: | DATE COMPLETED: |
|---|---|
| Peter Chen | January 3, 2005 |

cc: ANDA 76-703
Division File
Field Copy

Endorsements:

HFD-625/M.Smela M Smela 1/26/05

HFD-617/P.Chen Peter Chen 1/25/05

V:\FIRMSNZ\NOVEX\LTRS&REV\76703ta-ap.doc

Approval

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# BIOEQUIVALENCE REVIEWS

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 76-703 |
| **Drug Product Name** | Desmopressin Acetate Nasal Spray, 0.01mg/spray |
| **Strength** | 0.01mg/spray (0.01% solution) |
| **Applicant Name** | Novex Pharma |
| **Address** | 380 Elgin Mills Rd East<br>Richmond Hill, Ontario, Canada L4C 5H2 |
| **Submission Date(s)** | 26 March 2003 |
| **Amendment Date(s)** | NA |
| **Reviewer** | James L. Osterhout |
| **First Generic** | No |
| **File Location** | V:\firmsnz\novex\ltrs&rev\76703N0303 |

## I. Executive Summary

The application contains a request for waiver of in-vivo bioavailability requirements for Desmopressin Acetate Nasal Spray 0.01mg/spray (Nasal Solution 0.01%) 5mL bottle under 21 CFR 320.22(b)(3). The reference listed drug (RLD) is DDAVP® Nasal Spray (desmopressin acetate), available in a 5mL bottle with spray pump that delivers 10μg per actuation, from Aventis Pharmaceutical Incorporated (NDA 17-922-003).

The firm has submitted comparative formulations demonstrating that its Desmopressin Acetate Nasal Solution 0.01% and Aventis Pharmaceutical's DDAVP® Nasal Spray are qualitatively and quantitatively the same (Q1 & Q2) in support of the biowaiver request.

The application also contains comparability of container and closure systems, and in-vitro testing between the firm's Desmopressin Acetate Nasal Solution 0.01% and Aventis Pharmaceutical's DDAVP® Nasal Spray that demonstrate equivalent performance. The in-vitro testing includes single actuation content through container life, priming and re-priming, droplet size distribution by laser diffraction, droplet size distribution by cascade impactor, spray pattern, and plume geometry.

The firm did not perform spray pattern imaging at two distances at least three centimeters apart. The application is incomplete.

## II. Table of Contents

## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Desmopressin Acetate Nasal Solution (Nasal Spray) 0.01% |
| **Reference Product** | DDAVP® Nasal Spray 0.01mg / spray (needs no refrigeration) |
| **RLD Manufacturer** | Aventis Pharmaceuticals Inc. |
| **NDA No.** | N017922 (003 product) |
| **RLD Approval Date** | 07 August 1996 |
| **Indication** | Desmopressin Acetate Nasal Spray is indicated for the 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. |

### B. PK/PD Information

| | |
|---|---|
| **Bioavailability** | Desmopressin acetate administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection. |
| **Food Effect** | Not applicable |
| **Tmax** | Approximately 0.65 hours |
| **Metabolism** | Not available |
| **Excretion** | Not available |
| **Half-life** | The biphasic half-lives for intranasal desmopressin acetate nasal spray were 7.8 and 75.5 minutes for the fast and slow phases. |

| | |
|---|---|
| **Relevant OGD or DBE History** | **Controls 00-037, 01-055, & 01-405**: request for BE recommendations for subject #'s and if a different preservative could be used. The requirements of Q1 & Q2, container & closure sameness, and in-vitro testing were explained for BE determination. The requirement for in-vivo BE study and in-vitro testing stated if a different formulation from RLD is used.<br>**Control 02-141**: OGD processing of request to use the Bausch & Lomb product as RLD since the Aventis product was not available. Determination that Aventis was still marketing the refrigerated version of the product, which was not Q1 & Q2 with the non-refrigerated version.<br>**Control 02-165**: response to control 02-141 from firm reiterating that the RLD was not available and asking to use the B&L generic as RLD.<br>**ANDA 74-830**: submission by Bausch & Lomb for desmopressin acetate nasal spray. RLD was NDA 17-922-002, the non-refrigerated metered dose product. The application was acceptable.<br>**ANDA ——**: submission by ——— for desmopressin acetate nasal spray. RLD was NDA 17-922-002, the non-refrigerated metered dose product. The application was incomplete and withdrawn by the firm. This application does not ——— as the NDA 17922-002 product is not longer marketed. It was replaced by the NDA 17-922 003 product (needs no refrigeration). |
| **Agency Guidance** | There is no specific agency guidance for a desmopressin acetate nasal spray product. |
| **Drug Specific Issues** | None |

### C. Contents of Submission

| Studies | Y/N |
|---|---|
| **Single Actuation Content Through Container Life** | Y |
| **Priming and Re-priming** | Y |
| **Droplet Size Distribution by Laser Diffraction** | Y |
| **Drug in Small Particles / Droplets by Cascade Impactor** | Y |
| **Particle / Droplet Size Distribution by Cascade Impactor (aerosol only)** | N |
| **Drug Particle Size Distribution by Microscopy (suspension only)** | N |
| **Spray Pattern** | Y |
| **Plume Geometry** | Y |
| **Formulation Q1 & Q2** | Y |
| **Comparability in Container & Closure Systems** | Y |

### D. Waiver Request(s) For Other Strength

| | |
|---|---|
| **Strengths for which waivers requested** | None |
| **Regulation cited** | Not Applicable |
| **Test and reference are Q1 & Q2?** | Not Applicable |
| **Dissolution is acceptable?** | Not Applicable |
| **Waiver granted?** | Not Applicable |

### E. Formulation

| | |
|---|---|
| **Location in section IV. Appendix** | **See Table 29** |
| **Inactive ingredients within IIG Limits?** | YES |
| **If no, list ingredients outside of limits** | Not Applicable |
| **Formulation is acceptable?** | YES |
| **If not acceptable, why?** | Not Applicable |

### F. Container and Closure Systems

#### 1. Actuator & Pump Information

| | Test | Reference |
|---|---|---|
| **Supplier** | [redacted] | [redacted] |
| **Pump Description** | A white plastic metering spray pump with a clear plastic protection cap. The pump is fitted with a white nasal spray actuator. | A white plastic metering spray pump with a clear plastic protection cap. The pump is fitted with a white nasal spray actuator. |
| **Actuator Metrics** | | |
| **Height (mm)** | 35.00 mm | 34.13 mm |
| **Outer width (mm)** | 4.27 mm | 6.15 mm |
| **Inner width (mm)** | 1.73 mm | 3.10 mm |
| **Orifice diameter (um)** | 251.42 um | 282.50 um |
| **Dip Tube Length (mm)** | 35.12 mm | 49.31 mm |
| **Lot #1** | GC7300 | NA for solutions |
| **Lot #2** | GC7301 | NA for solutions |
| **Lot #3** | GC7302 | NA for solutions |

**Comments on actuator:**

Physical comparative data of the test and reference metering devices is provided in Volume 1.3, pages 472-488. According to the firm, the manufacturer of the metering device used (———) indicated that the pump used by the firm in their test batch is the same as used in the innovator product, ———. It should be noted that the dimensions of the test and reference actuators are not the same.

### 2. Container Information

The innovator product actuator is crimped onto a 5mL flat bottom glass container. The firm indicated that their actuator screws onto their container, which is a 5mL V-bottom glass container.

**Comments on container:**

The container is acceptable.

## G. Procedures and Information Applicable to All Tests

| Summary | |
|---|---|
| **Study No.** | Not Applicable |
| **Study Site(s)** | Novex Pharma<br>380 Elgin Mills Road East<br>Richmond Hill, Ontario, Canada L4C 5H2 |
| **Study Dates** | Not Applicable |
| **Number of Units Tested / Lot** | 10 |
| **Strength Tested** | 0.01mg/spray (50 doses of 10µg, 5mL bottle) |

| | | |
|---|---|---|
| **Test Lot #'s (expiration date)** | **Lot#** | 2X130 (no expiration date given) |
| | **Lot Size** | ——— |
| | **Sub-Lot #** | GC7300 actuator |
| | | GC7301 actuator |
| | | GC7302 actuator |
| | **Units Tested / Lot** | 10 |
| **Reference Lot #'s (expiration date)** | **Lot #1** | DB7018A (February 2004) |
| | **Lot #2** | CF6681A (June 2003) |
| | **Lot #3** | CM6923A (December 2003) |
| | **Units Tested / Lot** | 10 |

| | |
|---|---|
| **Actuation method** | [redacted] Automated Spray Pump Actuation |
| **SOP's submitted (Y/N)** | Yes (GM-143) Volume 1.1, pages 126-143 |
| **Dose time (msec)** | 20 ± 2 |
| **Return time (msec)** | 30 ± 5 |
| **Hold time (sec)** | 0.5 |
| **Actuation force (kg)** | 6.0 ± 0.5 |

| | |
|---|---|
| **Bioanalytical method** | TM-1218 Volume 1.1, pages 156-174 |
| **Analyte name** | desmopressin |
| **Internal standard** | Not Applicable |
| **Method description** | [redacted] |
| **Standard curve linearity (R2)** | [redacted] |
| **Limit of quantitation** | [redacted] |
| **Recovery (%CV)** | [redacted] (0.8%) |
| **Within day precision (%CV)** | 0.4% |
| **Between day precision range (%CV)** | 0.3% - 1.8% |
| **Accuracy (%)** | [redacted] |
| **Specificity** | Yes |
| **SOPs submitted** | Yes |
| **Bioanalytical method is acceptable** | Yes |

## H. In-Vitro Studies

### 1. Single Actuation Content through Container Life

The firm performed single actuation content through container life testing using the [redacted] Automated Spray Pump Actuator (for actuation data see Section IIIG). Since the label claim on this product is 50 actuations, each bottle of test and reference product was actuated a total of 60 times (including priming and re-priming).

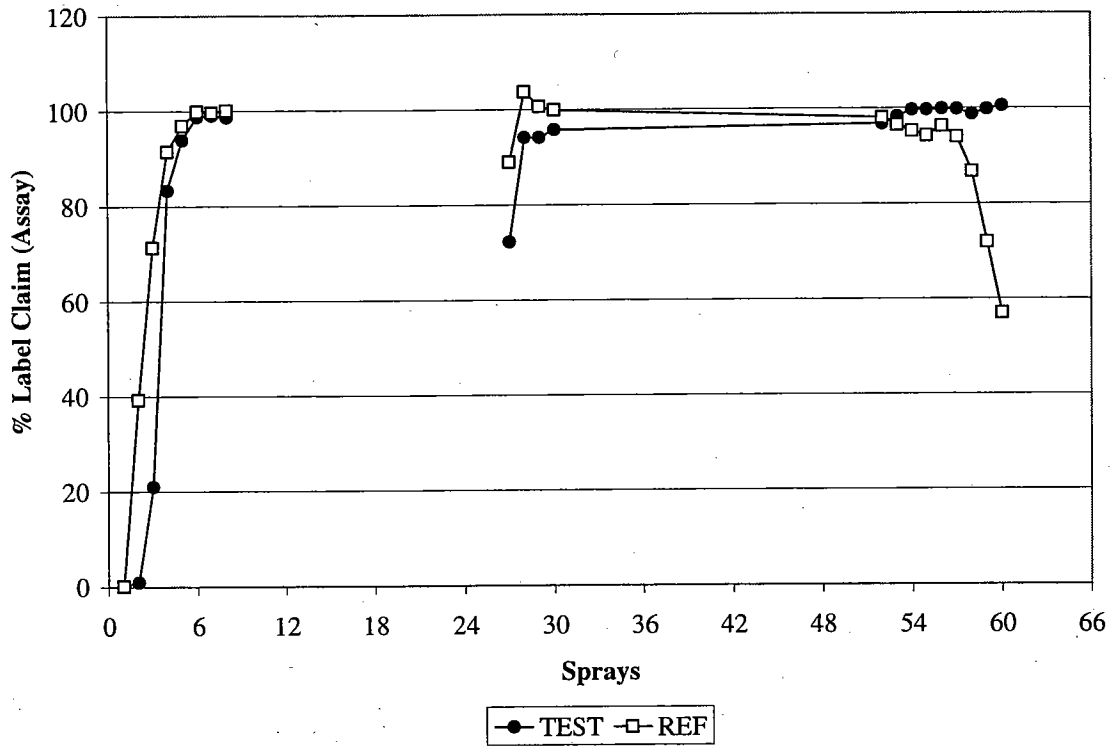
Each actuation was determined by the collected weight, as determined by the weight of a glass bottle prior to and after spray collection. In addition, the firm determined content by a [redacted] method (stability-indicating method). Ten units were tested for each test sub-lot and each reference lot. Therefore, for both the test and reference product, a total of 30 units were tested.

Content uniformity summary results were reported at the beginning of unit life (actuation #5) and end of unit life (actuation 54).

**Table 1: Unit Dose Summary Data**

| | | Spray # | Mean Arith | Mean Geo | N | Within Lot %CV Lot 1 | Within Lot %CV Lot 2 | Within Lot %CV Lot 3 | Between Lot %CV | Total | T /R Mean Arith | T /R Mean Geo | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TEST | Beg | 5 | 93.9 | 93.5 | 30 | 12.1 | 8.19 | 5.15 | 2.00 | 8.73 | 0.97 | 0.97 | 0.108 |
| | End | 54 | 99.7 | 99.6 | 30 | 5.49 | 2.36 | 3.96 | 0.44 | 4.02 | 1.05 | 1.05 | 0.029 |
| REF | Beg | 5 | 96.9 | 96.7 | 30 | 4.59 | 5.63 | 6.45 | 3.07 | 5.98 | | | |
| | End | 54 | 95.3 | 94.6 | 30 | 2.16 | 4.25 | 17.3 | 5.82 | 10.6 | | | |

**Figure 1: Single Actuation Content - Test & Reference**




**Comments on SAC through container life:**

The test product was 97% and 105% of the reference product in the beginning and end actuations respectively. The variability of the two products was comparable, with the notable exception of the reference product within lot variance at the end of life (Spray #54). This larger variability was not found when the actuations were performed through the container life at a 45° angle, as per the RLD label instructions (data not shown). The

test/reference ratios are within 90%-111%, used hitherto for acceptance of comparative in-vitro performance of nasal spray solutions.[1]

The firm provided actuation data based on each single spray as both weight and by a stability indicating method (TM-1218). Each bottle delivers 50 usable actuations of which none failed the first tier testing (10 units), with only one spray outside the 80-120 interval, and within the 75-125% interval (5th actuation Novex LOT#2X130 - GC7301).

Based on the mean values of the stability indicating analysis data, there was no change in the unit dose at the beginning (actuation #5) and end (actuation #54) sectors. There was no trend in the variability from the first primed actuation to the last actuation delivered per label claim.

There is a good correlation between the amount of drug delivered as measured by weight of spray and the amount of drug determined by ———. The variability in the weight assay method was lower in most cases than the——— method.

Based on the data submitted the test product is fully primed at the 5th actuation as per the RLD label claim. In addition, the test product delivers the RLD label indicated number of actuations (doses), that being 50.

**2. Priming and Re-priming**

The RLD label claims prime is achieved by the 5th actuation. The number of sprays required for prime was determined by assay of the first 5 actuations of each unit.

Both the test and reference products demonstrated prime by the 5th actuation in the firm's in vitro testing.

**Table 2: Priming Data - Test**

| Spray | Mean | | T / R | | | Within Lot CV% (N=10) | | | Between | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| # | Arith | Geo | Arith | Geo | N | Lot 1 | Lot 2 | Lot 3 | Lot CV% | CV% |
| 1 | 0.2 | NA | 1.10 | NA | 30 | 211 | 316 | 234 | 34.7 | 256 |
| 2 | 1.0 | NA | 0.02 | NA | 30 | NA | 287 | 316 | 156 | 468 |
| 3 | 21.0 | NA | 0.29 | NA | 29 | 98.3 | 127 | 116 | 24.1 | 111 |
| 4 | 83.3 | 82.5 | 0.91 | 0.90 | 30 | 13.5 | 17.8 | 5.73 | 2.75 | 12.9 |
| 5 | 93.9 | 93.5 | 0.97 | 0.97 | 30 | 12.1 | 8.19 | 5.15 | 2.00 | 8.73 |

See Table 17 for full reference data on priming

[1] Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

The RLD label also states that after 7 days of disuse (horizontal or vertical), the unit must be re-primed by wasting one actuation prior to use. The firm performed comparative re-priming in-vitro testing on the test and reference products (actuations 8-10 for horizontal and 27-29 for vertical position), which demonstrated that the firm's product need only be primed once prior to use (after 7 days if disuse), as indicated in the RLD label.

**Table 3: Test Data Re-priming Summary - Vertical 7 Days**

| | Lot# GC7300 | | Lot# GC7301 | | Lot# GC7302 | | Total (N=30) | |
|---|---|---|---|---|---|---|---|---|
| Spray # | AVG | %CV | AVG | %CV | AVG | %CV | AVG | %CV |
| 27 | 70.23 | 40.72 | 69.24 | 24.65 | 77.36 | 25.66 | 72.28 | 30.32 |
| 28 | 93.31 | 5.08 | 93.65 | 4.70 | 95.5 | 2.29 | 94.15 | 4.17 |
| 29 | 94.59 | 4.64 | 93.77 | 3.14 | 93.8 | 4.68 | 94.05 | 4.09 |

See Table 17 for Reference data on vertical re-priming

**Table 4: Test Data Re-priming Summary - Horizontal 7 Days**

| | Lot# GC7300 | | Lot# GC7301 | | Lot# GC7302 | | Total (N=9) | |
|---|---|---|---|---|---|---|---|---|
| Spray # | AVG | %CV | AVG | %CV | AVG | %CV | AVG | %CV |
| 8 | 90.6 | 2.34 | 75.3 | 31.26 | 86.2 | 5.54 | 84 | 16.5 |
| 9 | 91.3 | 0.46 | 88.7 | 2.97 | 96.1 | 4.13 | 92 | 4.39 |
| 10 | 92.2 | 3.72 | 93.4 | 2.15 | 97.6 | 0.95 | 94.4 | 3.37 |

The firm did not submit reference product data for horizontal re-priming.

### 3. Droplet Size Distribution by Laser Diffraction

Laser Diffraction was accomplished using the [redacted] spray droplet sizer synchronized with the [redacted] automated actuation system. Droplet size determination was performed at the beginning, middle, and end of use life of the product at 3mm, 5mm, and 8mm. Delay times at which data were obtained were based on the %transmission of the laser light, from plume formation (D10) to the intermediate stage (D50) to plume dissipation (D90).

| **Plume Region** | **Transmission Characteristics** |
|---|---|
| plume formation - initial | decreasing |
| plume fully formed - intermediate | stable (fully formed) |
| plume dissipation - end | increasing |

The three plume regions constituted the sampling points on which the data are based, and are different for each pump and actuation distance. The firm submitted D10, D50, D90, and SPAN data in their submission. The bioequivalence determination is based on the

D50 and SPAN data during the intermediate plume region, which represents the fully formed plume.

| | |
|---|---|
| Did the firm submit plume stage graphs for the test units? (Volume, pages?) | Yes, Vol. 1.2, pp. 346-400 |
| Did the firm submit plume stage graphs for the reference units? (Volume, pages?) | Yes, Vol. 1.2, pp. 401-455 |
| Are the plume stages acceptable? | Yes |

**Table 5: Droplet Size Distribution (D50) - Test Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV | T / R Arith Mean | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | GC7300 | GC7301 | GC7302 | | | | | |
| | 3 | Intermediate | 29.8 | 29.8 | 5.43 | 5.50 | 3.96 | 0.23 | 4.8 | 1.01 | 1.01 | 0.60 |
| Beg | 5 | Intermediate | 35.1 | 35.1 | 6.31 | 3.23 | 6.37 | 1.83 | 5.5 | 1.00 | 1.00 | 0.90 |
| | 8 | Intermediate | 44.9 | 44.8 | 7.23 | 6.24 | 6.46 | 1.27 | 6.5 | 1.02 | 1.02 | 0.27 |
| | 3 | Intermediate | 30.2 | 30.2 | 4.74 | 5.66 | 5.50 | 0.35 | 5.1 | 1.01 | 1.00 | 0.69 |
| Mid | 5 | Intermediate | 35.0 | 35.0 | 6.37 | 2.95 | 4.74 | 1.23 | 4.9 | 0.98 | 0.98 | 0.11 |
| | 8 | Intermediate | 45.8 | 45.7 | 5.84 | 7.60 | 4.97 | 1.84 | 6.2 | 1.03 | 1.03 | 0.06 |
| | 3 | Intermediate | 30.2 | 30.1 | 2.88 | 6.16 | 3.82 | 1.51 | 4.6 | 1.00 | 1.00 | 0.75 |
| End | 5 | Intermediate | 36.0 | 36.0 | 5.10 | 4.66 | 4.94 | 0.68 | 4.8 | 1.01 | 1.01 | 0.32 |
| | 8 | Intermediate | 45.1 | 45.0 | 7.39 | 6.37 | 4.42 | 2.34 | 6.3 | 1.02 | 1.02 | 0.44 |

**Table 6: Droplet Size Distribution (D50) - Reference Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CF6681A | CM6923A | DB7018A | | |
| | 3 | Intermediate | 29.6 | 29.6 | 5.06 | 3.43 | 3.81 | 2.33 | 4.48 |
| Beg | 5 | Intermediate | 35.1 | 35.0 | 3.58 | 3.99 | 5.34 | 2.11 | 4.55 |
| | 8 | Intermediate | 44.1 | 44.0 | 6.65 | 5.13 | 3.63 | 5.43 | 6.88 |
| | 3 | Intermediate | 30.1 | 30.1 | 5.35 | 2.79 | 4.31 | 1.83 | 4.42 |
| Mid | 5 | Intermediate | 35.7 | 35.6 | 4.21 | 2.66 | 3.86 | 2.55 | 4.11 |
| | 8 | Intermediate | 44.4 | 44.3 | 6.89 | 4.80 | 4.91 | 4.25 | 6.50 |
| | 3 | Intermediate | 30.3 | 30.3 | 5.62 | 3.84 | 4.04 | 1.58 | 4.62 |
| End | 5 | Intermediate | 35.6 | 35.6 | 4.74 | 3.02 | 4.85 | 1.52 | 4.33 |
| | 8 | Intermediate | 44.4 | 44.2 | 11.61 | 5.49 | 5.02 | 4.67 | 8.82 |

**Table 7: Droplet Size Distribution (SPAN) - Test Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV | T / R Arith Mean | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | GC7300 | GC7301 | GC7302 | | | | | |
| | 3 | Intermediate | 1.5 | 1.5 | 8.28 | 5.50 | 3.96 | 4.97 | 7.7 | 1.02 | 1.02 | 0.144 |
| Beg | 5 | Intermediate | 1.1 | 1.1 | 8.56 | 3.23 | 6.37 | 3.33 | 8.4 | 0.99 | 0.99 | 0.545 |
| | 8 | Intermediate | 1.0 | 1.0 | 8.05 | 6.24 | 6.46 | 5.05 | 10.1 | 0.93 | 0.93 | 0.003 |
| | 3 | Intermediate | 1.6 | 1.5 | 5.58 | 5.66 | 5.50 | 3.83 | 6.8 | 1.10 | 1.10 | 0.000 |
| Mid | 5 | Intermediate | 1.1 | 1.1 | 8.44 | 2.95 | 4.74 | 0.99 | 8.3 | 1.01 | 1.01 | 0.491 |
| | 8 | Intermediate | 1.0 | 1.0 | 8.54 | 7.60 | 4.97 | 1.66 | 8.9 | 0.94 | 0.94 | 0.006 |
| | 3 | Intermediate | 1.5 | 1.5 | 6.28 | 6.16 | 3.82 | 4.13 | 7.5 | 1.05 | 1.04 | 0.009 |
| End | 5 | Intermediate | 1.1 | 1.1 | 6.05 | 4.66 | 4.94 | 1.13 | 6.1 | 0.98 | 0.98 | 0.152 |
| | 8 | Intermediate | 0.99 | 0.98 | 10.88 | 6.37 | 4.42 | 4.83 | 11.29 | 0.86 | 0.87[2] | 0.00 |

**Table 8: Droplet Size Distribution (SPAN) - Reference Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CF6681A | CM6923A | DB7018A | | |
| | 3 | Intermediate | 1.4 | 1.4 | 3.66 | 4.91 | 5.04 | 2.09 | 4.73 |
| Beg | 5 | Intermediate | 1.1 | 1.1 | 5.59 | 4.59 | 5.19 | 1.21 | 5.07 |
| | 8 | Intermediate | 1.1 | 1.1 | 9.21 | 6.12 | 6.78 | 5.04 | 8.26 |
| | 3 | Intermediate | 1.4 | 1.4 | 5.29 | 4.70 | 5.97 | 2.33 | 5.52 |
| Mid | 5 | Intermediate | 1.1 | 1.1 | 5.16 | 4.29 | 3.94 | 0.97 | 4.41 |
| | 8 | Intermediate | 1.05 | 1.05 | 8.45 | 5.56 | 7.62 | 3.07 | 7.52 |
| | 3 | Intermediate | 1.4 | 1.4 | 4.82 | 5.85 | 3.66 | 2.02 | 4.97 |
| End | 5 | Intermediate | 1.1 | 1.1 | 4.85 | 6.16 | 4.21 | 1.90 | 5.18 |
| | 8 | Intermediate | 1.14 | 1.13 | 12.75 | 11.45 | 29.60 | 6.69 | 20.55[2] |

**Comments on Droplet Size Distribution by Laser Diffraction:**

The ratios of the test geometric means to the reference geometric means for D50 data at the intermediate stage of plume formation for the 3 distances provided (3cm, 5cm, and

[2] Population BE analysis was performed on the data to determine if the product would pass, as the reference product was highly variable. See I.D Additional Attachments p.36

8cm) are within the 90-111% range of acceptance (98-103%). For most of the comparisons of test to reference means the P-value was not significant.

The ratios of the test geometric means to the reference geometric means for SPAN data at the intermediate stage of plume formation for the 3 distances provided (3cm, 5cm, and 8cm) are within the 90-111% range of acceptance (93-110%), except for the 8cm distance at the end of life stage (87%). This was due to the reference product having a large actuation drug content variability at that distance (20.55%).[2] In addition, only the 3cm and 5cm distances are required to be analyzed for BE determination. For most of the comparisons of test to reference means the P-value was not significant.

With the exception of the above mentioned instance, the within-lot variability, between lot variability, and total variability were comparable between the test and reference products at the 3cm, 5cm, and 8cm distances for the intermediate plume stage.

The mean values of the D50 data did not change with the product life sectors. However, the D50 increased with the distance from actuation tip to laser beam from ~30 at 3cm to ~35 at 5cm to ~45 at 8cm distance.

The mean values of the total variability (%CV) was generally below 10% at the intermediate plume stage for both D50 and SPAN, with the D50 generally having a lower %CV than SPAN.

The geometric mean values of the T/R ratio at 3cm and 5cm distances for D50 and SPAN are within the 0.9-1.11 range used by the DBE for acceptance of in vitro performance of solution nasal products.

Therefore, based on the data in the above comments, distribution of droplets in the test product spray is similar to the reference product spray.

Plume Duration Data was also submitted and summarized for the beginning of life and end of life for the containers. This data is not required by the DBE for bioequivalence testing but is reviewed and summarized. See Table 22 and Table 23 below.

The Droplet Size Distribution by Laser Diffraction data are acceptable.

## 4. Drug in Small Particles / Droplets by Cascade Impactor

| Study Summary | |
|---|---|
| **Cascade impactor** | [redacted] |
| **Actuation Method** | [redacted] |
| **Flow Rate** | 28.3 ±5% L/min |

| Method Validation (Vol 1.1, pp 219-230) | |
|---|---|
| **Method Description** | [redacted] |
| **Accuracy** | [redacted] |
| **Intra-Day Precision (CV%)** | 2.1% |
| **Inter-Day Precision (CV%)** | 8.0% |
| **Sensitivity (CV%)** | [redacted] (2.4%) |
| **Linearity (R2)** | [redacted] |
| **Specificity** | YES |
| **Suitability** | 12.5%-7.9 CV%<br>100%-1.4 CV%<br>200%-0.7 CV% |
| **Limit of Quantitation (CV%)** | [redacted] (7.9%) |
| **Limit of Detection** | [redacted] |

| Collection Stages | | |
|---|---|---|
| Collection # | Stage(s) Involved | Aerodynamic Diameter (um) |
| 1 | stage 0 | > 9.0 um |
| 2 | stage 1 | < 9.0 um |
| 3 | stages 2-9 | < 4.7 um |

Collection #2 and #3 were combined for analysis of the data, as they represent the fine particles/droplets (>9um) as per the guidance for nasal sprays. The CV% was determined from the compilation data of the two stages.

[redacted]

Sprays #6 to #53 were fired into waste. The procedure was repeated for collection of the end of life spray (spray #54). The method was repeated for the remaining nine units.

**Table 9: Cascade Impaction - Material Recovered**

| TEST | Life Stage | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Mean ARITH | GEO | P |
|---|---|---|---|---|---|---|---|---|---|---|
| Group 1 | BEG | 96.60 | 3.13 | 2.31 | 2.82 | 1.39 | 2.91 | 1.01 | 1.01 | 0.446 |
| | END | 97.55 | 2.30 | 4.85 | 2.34 | 0.71 | 3.32 | 1.03 | 1.03 | 0.007 |
| Group 2 | BEG | 0.00 | NA | NA | NA | NA | NA | 0.00 | NA | NA |
| | END | 0.00 | NA | NA | NA | NA | NA | 0.00 | NA | NA |

| REF | Life Stage | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% |
|---|---|---|---|---|---|---|---|
| Group 1 | BEG | 95.87 | 4.68 | 4.76 | 4.52 | 0.60 | 4.52 |
| | END | 94.83 | 5.25 | 3.06 | 3.06 | 2.41 | 4.32 |
| Group 2 | BEG | 0.65 | 632.46 | NA | NA | 346.41 | 1076.87 |
| | END | 0.00 | NA | NA | NA | NA | NA |

NA: not applicable because division by zero or square root of zero errors.

**Comments on Drug in Small Particles / Droplets by Cascade Impaction:**

The results indicate that the amount of material deposited in droplets >9um is similar between the test product and reference product.

This fraction that is representative of fine particles is denoted as particles with a diameter less than 9um. This is determined by the amount of drug collected after Plate 0 of the cascade impactor apparatus (group 2). The amount of drug deposited in Group 2 constitutes less that 1% of the total drug per actuation collected from the apparatus, and is considered negligible when compared to the amount of drug deposited in Group 1.

Therefore, the bioequivalence determination may be based solely on the Group 1 Data.

[ ]

The amount of drug collected in Group 1 and Group 2 combined for the test product was 96.6% and 97.55% of label claim for the beginning and end of life actuations respectively. The amount of drug collected in Group 1 and Group 2 combined for the reference product was 96.52% and 94.83% of label claim for the beginning and end of life actuations respectively. This does not account for 100% of the label claim. However, these values correspond well with the drug recovered in Section I.H.1 above, Single Actuation Content through Container Life.

The Drug in Small Particles / Droplets by Cascade Impaction data are acceptable.

### 5. Particle / Droplet Size Distribution by Cascade Impactor

Not Applicable to this Product (Aerosol products only)

### 6. Drug Particle Size Distribution by Microscopy

Not Applicable to this Product (Suspension products only)

## 7. Spray Pattern

| Study Summary | |
|---|---|
| **Method Description** | digital image capture of laser diode sheet illuminated vertical cross-section of spray |
| **Visualization Apparatus** | [redacted] |
| **Actuation Apparatus** | [redacted] |
| **Spray Pattern Distance 1** | 3 cm |
| **Spray Pattern Distance 2** | 4 cm |
| **Spray Pattern Distance 3** | 5 cm |
| **20% of Spray Pattern Images Provided?** | YES |
| **If so, picture or digital file?** | digital file |
| **Metrics Determined by Software?** | YES |

| | | |
|---|---|---|
| **Method and Validation** | | Vol 1.1, pp 231-255 |
| **System precision - CV%** (at both distances) | **Dmax** | 0.9, 1.5, 1.9 |
| | **Dmin** | 1.6, 1.0, 1.0 |
| | **Ovality Ratio** | 1.1, 0.8, 1.9 |
| **Intra-day precision - CV%** (at both distances) | **Dmax** | 3.8, 7.0, 6.3 |
| | **Dmin** | 7.7, 3.6, 3.3 |
| | **Ovality Ratio** | 10.6, 6.5, 6.1 |
| **Inter-day precision - CV%** (at both distances) | **Dmax** | 3.3, 3.1, 2.5 |
| | **Dmin** | 4.1, 3.9, 2.7 |
| | **Ovality Ratio** | 1.1, 1.6, 1.8 |
| **Robustness (% Difference)** (at both distances) | **Dmax** | 8.1, 9.8, 12.1 |
| | **Dmin** | 0.5, 1.4, 0.8 |
| | **Ovality Ratio** | 7.6, 8.5, 12.7 |
| **Method Acceptable?** | | YES |

The firm submitted spray pattern data at three distances from the actuator tip to determine the maximum diameter (Dmax), minimum diameter (Dmin), and the ovality ratio (Dmax/Dmin). The firm provided 20% of the digital image files with the metrics indicated on the spray pattern visualizations in the application. For full summary data on Dmax, Dmin, and Ovality see Appendix A.7 Table 24 and Table 25.

**Table 10: Spray Pattern Ovality - Test and Reference Data**

**Test**

| Life Stage | Dist. (cm) | Metric | Arith. Mean | Geo Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T/R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BEG | 3 | Ovality | 1.27 | 1.27 | 6.72 | 7.73 | 4.17 | 3.51 | 6.88 | 0.972 | 0.143 |
| | 4 | Ovality | 1.36 | 1.35 | 4.97 | 10.64 | 9.54 | 5.13 | 9.61 | 0.988 | 0.620 |
| | 5 | Ovality | 1.48 | 1.47 | 11.97 | 16.68 | 10.36 | 3.36 | 13.25 | 0.966 | 0.324 |
| END | 3 | Ovality | 1.30 | 1.29 | 10.40 | 10.97 | 6.90 | 3.38 | 9.74 | 0.975 | 0.338 |
| | 4 | Ovality | 1.29 | 1.29 | 7.33 | 6.51 | 8.28 | 1.69 | 7.28 | 0.959 | 0.063 |
| | 5 | Ovality | 1.40 | 1.39 | 6.96 | 6.45 | 10.92 | 1.87 | 8.15 | 0.907 | 0.002 |

**Ref**

| Life Stage | Dist. (cm) | Metric | Arith. Mean | Geo Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% |
|---|---|---|---|---|---|---|---|---|---|
| BEG | 3 | Ovality | 1.31 | 1.30 | 6.48 | 5.96 | 9.64 | 4.43 | 8.26 |
| | 4 | Ovality | 1.37 | 1.37 | 9.89 | 8.69 | 14.24 | 4.42 | 11.56 |
| | 5 | Ovality | 1.53 | 1.52 | 9.64 | 10.35 | 17.07 | 3.15 | 12.80 |
| END | 3 | Ovality | 1.34 | 1.33 | 8.15 | 7.15 | 17.78 | 2.79 | 11.97 |
| | 4 | Ovality | 1.35 | 1.35 | 9.64 | 6.66 | 14.95 | 0.41 | 10.56 |
| | 5 | Ovality | 1.55 | 1.54 | 13.64 | 14.59 | 17.69 | 2.01 | 15.01 |

For full data of ovality ration Dmax and Dmin, see Appendix A.7 Spray Pattern.

**Comments on Spray Pattern:**

The ratios of the test geometric means to the reference geometric means for the ovality metric were within the 0.9-1.11 acceptance range for both beginning (spray #5) and end of product life (spray#54) actuations. It should be noted that the ratios of the test geometric means to the reference geometric means for the Dmax and Dmin metrics were not within the 0.9-1.11 acceptance range for both beginning and end of product life. Furthermore, the spray pattern distances were not at least 3cm apart (only 1cm apart).

In the 20% of the spray pattern images submitted, none of the Dmax vector lines cross the spray pattern boundary. Weighted center of mass values were obtained, and in the spray pattern data submitted generally corresponded well with the un-weighted center of mass values. All of the spray pattern outline boundaries were acceptable and generally corresponded to the computed fitted oval boundary. The Dmax and Dmin values analyzed in this review were calculated automatically from the outline boundaries (true shape). The Dmax and Dmin values for the fitted oval boundaries were also automatically calculated and resulted similar in values.

The spray pattern data is incomplete. The firm should perform spray pattern testing at 2 distances within the range of 3cm to 7cm, that are at least 3cm apart. The firm can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for BE evaluation. Alternatively, the firm can use automated analysis of the area and ovality ratios of the test and reference products at the beginning of life stage for BE evaluation.

### 8. Plume Geometry

| Study Summary | |
|---|---|
| **Method Description** | digital image capture of laser illuminated side view of spray plume |
| **Visualization Apparatus** | [redacted] |
| **Actuation Apparatus** | [redacted] |
| **Image Delay Time - Plume Initiation** | 10 ms |
| **Image Delay Time - Plume Formation** | 50 ms |
| **Image Delay Time - Plume Dissipation** | > 50 ms |
| **Camera Distance from Actuator Orifice** | 34 cm |
| **20% of Plume Geometry Images Provided?** | YES |
| **Method of Plume Angle Determination? (manual / software)** | Software |
| **Method of Plume Height Determination? (manual / software)** | Manual |

| **Method and Validation** | | Vol 1.1, pp 268-277 |
|---|---|---|
| **System precision - CV% (initiation, formation, dissipation)** | **Plume Angle** | 3.9, 3.1, 3.3 |
| | **Plume Height** | 8.1, 4.8, 21.2 |
| | **Plume Width** | 3.5, 2.4, 5.9 |
| **Intra-day precision - CV% (initiation, formation, dissipation)** | **Plume Angle** | 10.7, 10.1, 15.9 |
| | **Plume Height** | 20.1, 15.3, 24.1 |
| | **Plume Width** | 20.8, 6.2, 41.8 |
| **Inter-day precision - CV% (initiation, formation, dissipation)** | **Plume Angle** | 5.6, 4.4, 5.7 |
| | **Plume Height** | 8.7, 5.0, 16.5 |
| | **Plume Width** | 7.3, 6.8, 12.2 |
| **Robustness Performed?** | | YES |
| **Method Acceptable?** | | YES |

Reviewer's Note: validation data for 0 degree view only.

The firm characterized the geometry of the test and reference plume by measuring the plume angle at plume initiation, plume formation, and plume dissipation. In addition, the firm further characterized the plume geometry by determining the plume width and length at plume initiation and plume formation. All of these tests were performed on beginning life stage actuations (spray #5) with digital imaging at both 0 degrees and 90 degrees, perpendicular to the axis of spray.

**Table 11: Plume Angle Data - 0° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 82.2 | 1.59 | 2.88 | 1.35 | 0.5 | 2.0 | 1.01 | 0.1234 |
| | Formation | 91.2 | 0.58 | 2.53 | 0.49 | 0.4 | 1.5 | 0.99 | 0.1229 |
| | Dissipation | 69.1 | 1.23 | 1.59 | 1.48 | 0.8 | 1.5 | 1.00 | 0.3337 |
| REF | Initiation | 81.7 | 1.04 | 1.15 | 1.00 | 0.2 | 1.0 | | |
| | Formation | 91.6 | 0.80 | 1.07 | 0.71 | 0.4 | 0.9 | | |
| | Dissipation | 69.4 | 1.53 | 1.67 | 1.64 | 0.6 | 1.6 | | |

**Table 12: Plume Height Data - 0° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 44.9 | 18.57 | 17.15 | 9.31 | 2.8 | 15.0 | 1.12 | 0.004 |
| | Formation | 134.4 | 3.65 | 2.53 | 0.49 | 1.1 | 3.4 | 1.00 | 0.749 |
| REF | Initiation | 40.0 | 14.50 | 10.94 | 17.38 | 4.0 | 14.3 | | |
| | Formation | 134.1 | 2.94 | 2.27 | 3.16 | 0.6 | 2.8 | | |

**Table 13: Plume Width Data - 0° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 29.4 | 6.70 | 9.31 | 3.91 | 1.6 | 6.8 | 1.04 | 0.0435 |
| | Formation | 84.8 | 2.03 | 8.49 | 1.84 | 1.2 | 5.0 | 1.01 | 0.4132 |
| REF | Initiation | 28.60 | 7.91 | 10.81 | 4.38 | 1.9 | 8.0 | | |
| | Formation | 85.36 | 3.07 | 4.96 | 7.39 | 1.5 | 5.4 | | |

**Comments on Plume Geometry:**

The ratios of the test geometric means to the reference geometric means for the overall angle metric are within the 0.9-1.11 acceptance range at the plume formation, initiation, and dissipation sections. The values ranged from 0.995-1.006.

The ratios of the test geometric means to the reference geometric means for the plume height metric are within the 0.9-1.11 acceptance range at the plume formation section (1.00 ratio) but not the plume initiation section (1.12 ratio). The ratios of the test geometric means to the reference geometric means for the plume width metric are within the 0.9-1.11 acceptance range at the plume formation and plume initiation sections. Data for plume height and width were not submitted at the plume dissipation stage.

In the 20% of the plume geometry images submitted, all of the angle vector lines were indicative of actual plume spray angle. In addition, the plume width lines, which were manually determined, extend into the lower density regions of the plume.

The current draft guidance for nasal sprays[1] does not require that the plume height or plume width meet a BE test for acceptance of the test product. For comprehensive data tables of plume angle, height, and width from the 90 degree view angle, see Appendix A.8. Table 26, Table 27, and Table 28.

The plume geometry data at 34cm distance is acceptable.

## I. Deficiency Comments

1. The firm did not provide an expiration date for the test lot.

2. The spray pattern distances were not at least 3cm apart. The firm should perform spray pattern testing at 2 distances within the range of 3cm to 7cm, that are at least 3cm apart. The firm can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for BE evaluation. Alternatively, the firm can use automated analysis of the area and ovality ratios of the test and reference products at the beginning of life stage for BE evaluation.

## J. Recommendations

The in-vitro performance data submitted by Novex Pharma on the test product Desmopressin Acetate Nasal Solution (Nasal Spray) 0.01% Lot #2X130, comparing it with the RLD product, Aventis Pharmaceutical's DDAVP® Nasal Spray Lot #s CF6681A, CM6923A, and DB7018A has been found incomplete by the Division of Bioequivalence.

James Osterhout, Reviewer, Branch I — Date 4/27/04

Shriniwas G. Nerurkar, Team Leader, Branch I — Date 5/28/2004

Dale P. Conner, Pharm. D. — Date 5/28/04
Director, Division of Bioequivalence
Office of Generic Drugs

# IV. Appendix

## A. In-Vitro Studies Data

### 1. Single Actuation Content through Container Life

**Table 14: Test Data Summary**

| | Spray | Mean | | T / R | | | Within Lot %CV | | | Between | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # | Arith | Geo | Arith | Geo | N | Lot 1 | Lot 2 | Lot 3 | Lot %CV | %CV | P |
| Priming | 1 | 0.2 | NA | 1.10 | NA | 30 | 211 | 316 | 234 | 34.7 | 256 | 0.897 |
| | 2 | 1.0 | NA | 0.02 | NA | 30 | NA | 287 | 316 | 156 | 468 | 0.000 |
| | 3 | 21.0 | NA | 0.29 | NA | 29 | 98.3 | 127 | 116 | 24.1 | 111 | 0.000 |
| | 4 | 83.3 | 82.5 | 0.91 | 0.90 | 30 | 13.5 | 17.8 | 5.73 | 2.75 | 12.9 | 0.001 |
| | 5 | 93.9 | 93.5 | 0.97 | 0.97 | 30 | 12.1 | 8.19 | 5.15 | 2.00 | 8.73 | 0.108 |
| | 6 | 98.8 | 98.5 | 0.99 | 0.99 | 30 | 11.4 | 3.42 | 2.89 | 3.62 | 7.26 | 0.470 |
| | 7 | 99.1 | 98.9 | 0.99 | 0.99 | 30 | 9.18 | 2.66 | 3.42 | 3.41 | 6.18 | 0.637 |
| | 8 | 98.7 | 98.6 | 0.99 | 0.99 | 9 | 4.67 | 1.87 | 2.77 | 0.56 | 2.90 | 0.554 |
| Re-Priming | 27 | 72.3 | 66.3 | 0.81 | 0.75 | 30 | 40.7 | 24.6 | 25.7 | 6.13 | 30.3 | 0.000 |
| | 28 | 94.2 | 94.1 | 0.91 | 0.91 | 30 | 5.08 | 4.70 | 2.29 | 1.25 | 4.17 | 0.000 |
| | 29 | 94.1 | 94.1 | 0.94 | 0.93 | 30 | 4.64 | 2.70 | 4.68 | 0.49 | 3.99 | 0.000 |
| | 30 | 95.7 | 95.7 | 0.96 | 0.96 | 9 | 6.96 | 1.31 | 2.13 | 1.98 | 4.12 | 0.042 |
| Tail-Off | 52 | 96.8 | 96.8 | 0.99 | 0.99 | 9 | 1.84 | 2.83 | 2.30 | 1.15 | 2.27 | 0.299 |
| | 53 | 98.3 | 98.2 | 1.02 | 1.02 | 30 | 2.68 | 7.86 | 1.62 | 0.99 | 4.75 | 0.183 |
| | 54 | 99.7 | 99.6 | 1.05 | 1.05 | 30 | 5.49 | 2.36 | 3.96 | 0.44 | 4.02 | 0.029 |
| | 55 | 99.7 | 99.6 | 1.06 | 1.07 | 30 | 3.96 | 2.58 | 2.91 | 1.00 | 3.20 | 0.035 |
| | 56 | 99.9 | 99.8 | 1.04 | 1.04 | 30 | 3.92 | 2.22 | 1.81 | 0.43 | 2.72 | 0.012 |
| | 57 | 99.8 | 99.7 | 1.06 | 1.07 | 29 | 4.48 | 5.54 | 1.79 | 0.09 | 4.03 | 0.002 |
| | 58 | 98.8 | 98.7 | 1.14 | 1.16 | 30 | 6.23 | 3.76 | 2.12 | 1.71 | 4.42 | 0.000 |
| | 59 | 99.8 | 99.7 | 1.39 | 1.46 | 30 | 3.18 | 2.60 | 1.96 | 1.03 | 2.67 | 0.000 |
| | 60 | 100 | 100 | 1.76 | NA | 30 | 3.23 | 2.50 | 1.54 | 0.80 | 2.52 | 0.000 |

**Table 15: Reference Data Summary**

| | Spray | Mean | | | Within Lot %CV | | | Between | Total |
|---|---|---|---|---|---|---|---|---|---|
| | # | Arith | Geo | N | Lot 1 | Lot 2 | Lot 3 | Lot %CV | %CV |
| Priming | 1 | 0.2 | NA | 30 | 316 | 316 | 316 | 39.8 | 323 |
| | 2 | 39.3 | NA | 30 | 49.5 | 94.1 | 41.3 | 34.3 | 60.5 |
| | 3 | 71.3 | 65.4 | 30 | 7.65 | 53.4 | 16.7 | 18.1 | 30.3 |
| | 4 | 91.5 | 91.2 | 30 | 7.97 | 5.71 | 8.16 | 1.42 | 7.20 |
| | 5 | 96.9 | 96.7 | 30 | 4.59 | 5.63 | 6.45 | 3.07 | 5.98 |
| | 6 | 100 | 99.8 | 30 | 4.07 | 6.25 | 4.43 | 2.24 | 5.21 |
| | 7 | 99.7 | 99.6 | 30 | 1.78 | 5.01 | 3.50 | 0.96 | 3.64 |
| | 8 | 100 | 99.9 | 9 | 4.16 | 5.32 | 2.42 | 6.19 | 6.51 |
| Re-Priming | 27 | 89.0 | 88.9 | 28 | 3.59 | 3.91 | 4.07 | 0.50 | 3.74 |
| | 28 | 104 | 104 | 30 | 2.28 | 5.65 | 3.24 | 0.74 | 3.88 |
| | 29 | 101 | 101 | 30 | 1.59 | 1.83 | 4.85 | 0.93 | 3.10 |
| | 30 | 99.9 | 99.8 | 11 | 6.58 | 2.70 | 3.80 | 2.86 | 4.46 |
| Tail-Off | 52 | 98.1 | 98.0 | 9 | 2.97 | 1.25 | 1.97 | 2.29 | 2.74 |
| | 53 | 96.5 | 96.4 | 30 | 1.79 | 2.26 | 8.98 | 3.23 | 5.76 |
| | 54 | 95.3 | 94.6 | 30 | 2.16 | 4.25 | 17.3 | 5.82 | 10.6 |
| | 55 | 94.3 | 93.1 | 30 | 5.80 | 5.16 | 22.9 | 8.22 | 14.1 |
| | 56 | 96.2 | 95.9 | 30 | 4.35 | 2.14 | 11.6 | 3.50 | 7.41 |
| | 57 | 94.0 | 93.5 | 30 | 12.2 | 5.04 | 8.61 | 3.98 | 9.24 |
| | 58 | 86.7 | 85.0 | 30 | 24.7 | 5.7 | 17.1 | 12.2 | 18.8 |
| | 59 | 71.9 | 68.4 | 29 | 18.3 | 10.8 | 29.8 | 26.4 | 30.3 |
| | 60 | 56.9 | NA | 30 | 36.7 | 25.0 | 35.5 | 34.3 | 42.0 |

## 2. Priming and Re-priming

**Table 16: Test Data**

| Spray # | Mean | | T / R | | N | Within Lot CV% (N=10) | | | Between Lot CV% | Total CV% |
|---|---|---|---|---|---|---|---|---|---|---|
| | Arith | Geo | Arith | Geo | | Lot 1 | Lot 2 | Lot 3 | | |
| 1 | 0.2 | NA | 1.10 | NA | 30 | 211 | 316 | 234 | 34.7 | 256 |
| 2 | 1.0 | NA | 0.02 | NA | 30 | NA | 287 | 316 | 156 | 468 |
| 3 | 21.0 | NA | 0.29 | NA | 29 | 98.3 | 127 | 116 | 24.1 | 111 |
| 4 | 83.3 | 82.5 | 0.91 | 0.90 | 30 | 13.5 | 17.8 | 5.73 | 2.75 | 12.9 |
| 5 | 93.9 | 93.5 | 0.97 | 0.97 | 30 | 12.1 | 8.19 | 5.15 | 2.00 | 8.73 |
| 6 | 98.8 | 98.5 | 0.99 | 0.99 | 30 | 11.42 | 3.42 | 2.89 | 3.62 | 7.26 |
| 7 | 99.1 | 98.9 | 0.99 | 0.99 | 30 | 9.18 | 2.66 | 3.42 | 3.41 | 6.18 |
| 8 | 98.7 | 98.6 | 0.99 | 0.99 | 9 | 4.67 | 1.87 | 2.77 | 0.56 | 2.90 |
| 27 | 72.3 | 66.3 | 0.81 | 0.75 | 30 | 40.72 | 24.65 | 25.66 | 6.13 | 30.32 |
| 28 | 94.2 | 94.1 | 0.91 | 0.91 | 30 | 5.08 | 4.70 | 2.29 | 1.25 | 4.17 |
| 29 | 94.1 | 94.1 | 0.94 | 0.93 | 30 | 4.64 | 2.70 | 4.68 | 0.49 | 3.99 |
| 30 | 95.7 | 95.7 | 0.96 | 0.96 | 9 | 6.96 | 1.31 | 2.13 | 1.98 | 4.12 |
| 52 | 96.8 | 96.8 | 0.99 | 0.99 | 9 | 1.84 | 2.83 | 2.30 | 1.15 | 2.27 |
| 53 | 98.3 | 98.2 | 1.02 | 1.02 | 30 | 2.68 | 7.86 | 1.62 | 0.99 | 4.75 |
| 54 | 99.7 | 99.6 | 1.05 | 1.05 | 30 | 5.49 | 2.36 | 3.96 | 0.44 | 4.02 |
| 55 | 99.7 | 99.6 | 1.06 | 1.07 | 30 | 3.96 | 2.58 | 2.91 | 1.00 | 3.20 |
| 56 | 99.9 | 99.8 | 1.04 | 1.04 | 30 | 3.92 | 2.22 | 1.81 | 0.43 | 2.72 |
| 57 | 99.8 | 99.7 | 1.06 | 1.07 | 29 | 4.48 | 5.54 | 1.79 | 0.09 | 4.03 |
| 58 | 98.8 | 98.7 | 1.14 | 1.16 | 30 | 6.23 | 3.76 | 2.12 | 1.71 | 4.42 |
| 59 | 99.8 | 99.7 | 1.39 | 1.46 | 30 | 3.18 | 2.60 | 1.96 | 1.03 | 2.67 |
| 60 | 100.5 | 100.4 | 1.76 | #NUM! | 30 | 3.23 | 2.50 | 1.54 | 0.80 | 2.52 |

**Table 17: Reference Data**

| Spray # | Mean Arith | Mean Geo | N | Within Lot CV% (N=10) Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.2 | NA | 30 | 316.2 | 316.2 | 316.2 | 39.8 | 322.6 |
| 2 | 39.3 | NA | 30 | 49.5 | 94.1 | 41.3 | 34.3 | 60.5 |
| 3 | 71.3 | 65.4 | 30 | 7.65 | 53.38 | 16.71 | 18.11 | 30.30 |
| 4 | 91.5 | 91.2 | 30 | 7.97 | 5.71 | 8.16 | 1.42 | 7.20 |
| 5 | 96.9 | 96.7 | 30 | 4.59 | 5.63 | 6.45 | 3.07 | 5.98 |
| 6 | 100.0 | 99.8 | 30 | 4.07 | 6.25 | 4.43 | 2.24 | 5.21 |
| 7 | 99.7 | 99.6 | 30 | 1.78 | 5.01 | 3.50 | 0.96 | 3.64 |
| 8 | 100.1 | 99.9 | 9 | 4.16 | 5.32 | 2.42 | 6.19 | 6.51 |
| 30 | 89.0 | 88.9 | 28 | 3.59 | 3.91 | 4.07 | 0.50 | 3.74 |
| 52 | 103.8 | 103.7 | 30 | 2.28 | 5.65 | 3.24 | 0.74 | 3.88 |
| 53 | 100.7 | 100.6 | 30 | 1.59 | 1.83 | 4.85 | 0.93 | 3.10 |
| 54 | 99.9 | 99.8 | 11 | 6.58 | 2.70 | 3.80 | 2.86 | 4.46 |
| 55 | 98.1 | 98.0 | 9 | 2.97 | 1.25 | 1.97 | 2.29 | 2.74 |
| 56 | 96.5 | 96.4 | 30 | 1.79 | 2.26 | 8.98 | 3.23 | 5.76 |
| 57 | 95.3 | 94.6 | 30 | 2.16 | 4.25 | 17.31 | 5.82 | 10.58 |
| 58 | 94.3 | 93.1 | 30 | 5.80 | 5.16 | 22.87 | 8.22 | 14.15 |
| 59 | 96.2 | 95.9 | 30 | 4.35 | 2.14 | 11.65 | 3.50 | 7.41 |
| 60 | 94.0 | 93.5 | 30 | 12.21 | 5.04 | 8.61 | 3.98 | 9.24 |

### 3. Droplet Size Distribution by Laser Diffraction

**Table 18: Droplet Size Distribution (D50) - Test Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV GC7300 | GC7301 | GC7302 | Between Lot %CV | Total %CV | T / R Arith Mean | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Beg | 3 | Formation | 35.9 | 35.4 | 21.59 | 26.09 | 6.82 | 6.89 | 20.7 | 0.99 | 1.00 | 0.91 |
| | 3 | Intermediate | 29.8 | 29.8 | 5.43 | 5.50 | 3.96 | 0.23 | 4.8 | 1.01 | 1.01 | 0.60 |
| | 3 | Dissipation | 59.9 | 58.3 | 20.25 | 24.71 | 20.75 | 11.85 | 23.6 | 1.07 | 1.07 | 0.30 |
| | 5 | Formation | 39.8 | 39.6 | 8.48 | 10.48 | 13.06 | 0.55 | 10.5 | 1.01 | 1.01 | 0.79 |
| | 5 | Intermediate | 35.1 | 35.1 | 6.31 | 3.23 | 6.37 | 1.83 | 5.5 | 1.00 | 1.00 | 0.90 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | Dissipation | 39.5 | 39.4 | 6.60 | 5.08 | 6.09 | 2.76 | 6.2 | 0.99 | 0.99 | 0.53 |
| | 8 | Formation | 49.2 | 49.0 | 9.29 | 10.21 | 5.71 | 0.15 | 8.3 | 1.04 | 1.04 | 0.19 |
| | 8 | Intermediate | 44.9 | 44.8 | 7.23 | 6.24 | 6.46 | 1.27 | 6.5 | 1.02 | 1.02 | 0.27 |
| | 8 | Dissipation | 48.5 | 48.4 | 6.52 | 8.04 | 6.88 | 1.26 | 7.0 | 1.00 | 1.00 | 0.92 |
| | 3 | Formation | 36.4 | 36.2 | 9.53 | 15.23 | 8.86 | 0.98 | 11.2 | 0.98 | 0.99 | 0.64 |
| | 3 | Intermediate | 30.2 | 30.2 | 4.74 | 5.66 | 5.50 | 0.35 | 5.1 | 1.01 | 1.00 | 0.69 |
| | 3 | Dissipation | 38.4 | 38.2 | 8.41 | 14.02 | 9.40 | 2.06 | 10.6 | 0.87 | 0.89 | 0.01 |
| | 5 | Formation | 39.9 | 39.8 | 6.83 | 4.93 | 5.01 | 1.84 | 5.7 | 0.97 | 0.98 | 0.25 |
| Mid | 5 | Intermediate | 35.0 | 35.0 | 6.37 | 2.95 | 4.74 | 1.23 | 4.9 | 0.98 | 0.98 | 0.11 |
| | 5 | Dissipation | 36.9 | 36.8 | 4.18 | 4.80 | 9.52 | 0.70 | 6.4 | 0.93 | 0.93 | 0.00 |
| | 8 | Formation | 51.8 | 51.6 | 7.34 | 12.56 | 4.21 | 3.60 | 8.8 | 1.05 | 1.05 | 0.07 |
| | 8 | Intermediate | 45.8 | 45.7 | 5.84 | 7.60 | 4.97 | 1.84 | 6.2 | 1.03 | 1.03 | 0.06 |
| | 8 | Dissipation | 48.1 | 48.0 | 6.93 | 6.14 | 6.72 | 2.13 | 6.6 | 0.98 | 0.98 | 0.25 |
| | 3 | Formation | 36.5 | 36.4 | 7.54 | 14.24 | 5.18 | 3.20 | 10.0 | 0.90 | 0.92 | 0.07 |
| | 3 | Intermediate | 30.2 | 30.1 | 2.88 | 6.16 | 3.82 | 1.51 | 4.6 | 1.00 | 1.00 | 0.75 |
| | 3 | Dissipation | 34.6 | 34.5 | 11.26 | 6.53 | 4.76 | 1.02 | 7.7 | 0.79 | 0.80 | 0.00 |
| | 5 | Formation | 41.2 | 41.1 | 7.08 | 9.89 | 5.85 | 0.51 | 7.5 | 0.99 | 0.99 | 0.61 |
| End | 5 | Intermediate | 36.0 | 36.0 | 5.10 | 4.66 | 4.94 | 0.68 | 4.8 | 1.01 | 1.01 | 0.32 |
| | 5 | Dissipation | 38.3 | 38.2 | 5.09 | 7.39 | 9.54 | 2.05 | 7.5 | 0.96 | 0.96 | 0.02 |
| | 8 | Formation | 49.0 | 48.4 | 7.56 | 8.38 | 21.99 | 3.92 | 13.8 | 0.98 | 0.98 | 0.61 |
| | 8 | Intermediate | 45.1 | 45.0 | 7.39 | 6.37 | 4.42 | 2.34 | 6.3 | 1.02 | 1.02 | 0.44 |
| | 8 | Dissipation | 48.2 | 48.1 | 3.13 | 6.56 | 4.25 | 3.84 | 5.6 | 0.95 | 0.95 | 0.01 |

**Table 19: Droplet Size Distribution (D50) - Reference Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CF6681A | CM6923A | DB7018A | | |
| | 3 | Formation | 36.2 | 35.5 | 28.02 | 4.27 | 9.55 | 15.15 | 22.87 |
| | 3 | Intermediate | 29.6 | 29.6 | 5.06 | 3.43 | 3.81 | 2.33 | 4.48 |
| | 3 | Dissipation | 56.2 | 54.6 | 17.59 | 27.83 | 26.38 | 7.72 | 24.09 |
| | 5 | Formation | 39.5 | 39.3 | 13.09 | 4.45 | 6.22 | 7.50 | 10.86 |
| Beg | 5 | Intermediate | 35.1 | 35.0 | 3.58 | 3.99 | 5.34 | 2.11 | 4.55 |
| | 5 | Dissipation | 39.8 | 39.8 | 3.91 | 4.66 | 3.37 | 0.73 | 3.92 |
| | 8 | Formation | 47.5 | 47.2 | 10.38 | 6.99 | 6.38 | 9.77 | 11.49 |
| | 8 | Intermediate | 44.1 | 44.0 | 6.65 | 5.13 | 3.63 | 5.43 | 6.88 |
| | 8 | Dissipation | 48.4 | 48.3 | 4.43 | 3.38 | 5.26 | 2.52 | 4.75 |
| | 3 | Formation | 37.1 | 36.5 | 21.69 | 3.06 | 8.10 | 14.58 | 19.11 |
| | 3 | Intermediate | 30.1 | 30.1 | 5.35 | 2.79 | 4.31 | 1.83 | 4.42 |
| | 3 | Dissipation | 44.0 | 43.1 | 34.31 | 11.13 | 19.51 | 4.66 | 23.60 |
| | 5 | Formation | 41.0 | 40.8 | 11.93 | 5.11 | 6.31 | 9.33 | 11.49 |
| Mid | 5 | Intermediate | 35.7 | 35.6 | 4.21 | 2.66 | 3.86 | 2.55 | 4.11 |
| | 5 | Dissipation | 39.8 | 39.8 | 3.46 | 4.42 | 3.73 | 1.35 | 3.91 |
| | 8 | Formation | 49.4 | 49.1 | 13.15 | 6.36 | 6.23 | 7.56 | 11.19 |
| | 8 | Intermediate | 44.4 | 44.3 | 6.89 | 4.80 | 4.91 | 4.25 | 6.50 |
| | 8 | Dissipation | 48.9 | 48.8 | 4.04 | 3.78 | 3.85 | 2.63 | 4.34 |
| | 3 | Formation | 40.6 | 39.4 | 26.38 | 34.42 | 5.61 | 15.47 | 28.58 |
| | 3 | Intermediate | 30.3 | 30.3 | 5.62 | 3.84 | 4.04 | 1.58 | 4.62 |
| | 3 | Dissipation | 43.9 | 42.9 | 20.99 | 12.50 | 27.19 | 11.51 | 23.48 |
| | 5 | Formation | 41.7 | 41.5 | 10.01 | 9.17 | 7.10 | 7.99 | 10.93 |
| End | 5 | Intermediate | 35.6 | 35.6 | 4.74 | 3.02 | 4.85 | 1.52 | 4.33 |
| | 5 | Dissipation | 40.0 | 39.9 | 5.15 | 4.09 | 7.93 | 0.59 | 5.77 |
| | 8 | Formation | 49.9 | 49.5 | 16.19 | 10.43 | 6.39 | 7.52 | 13.29 |
| | 8 | Intermediate | 44.4 | 44.2 | 11.61 | 5.49 | 5.02 | 4.67 | 8.82 |
| | 8 | Dissipation | 50.6 | 50.4 | 7.28 | 6.68 | 10.37 | 2.47 | 8.21 |

**Table 20: Droplet Size Distribution (SPAN) - Reference Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV | T / R Arith Mean | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | GC7300 | GC7301 | GC7302 | | | | | |
| | 3 | Formation | 2.4 | 2.3 | 32.37 | 26.09 | 6.82 | 9.20 | 32.7 | 0.93 | 0.92 | 0.383 |
| | 3 | Intermediate | 1.5 | 1.5 | 8.28 | 5.50 | 3.96 | 4.97 | 7.7 | 1.02 | 1.02 | 0.144 |
| | 3 | Dissipation | 2.8 | 2.8 | 15.11 | 24.71 | 20.75 | 7.99 | 17.5 | 0.91 | 0.91 | 0.062 |
| | 5 | Formation | 1.5 | 1.5 | 25.57 | 10.48 | 13.06 | 3.83 | 30.9 | 1.00 | 0.98 | 0.947 |
| Beg | 5 | Intermediate | 1.1 | 1.1 | 8.56 | 3.23 | 6.37 | 3.33 | 8.4 | 0.99 | 0.99 | 0.545 |
| | 5 | Dissipation | 2.7 | 2.6 | 28.02 | 5.08 | 6.09 | 4.95 | 27.6 | 1.17 | 1.18 | 0.031 |
| | 8 | Formation | 1.1 | 1.0 | 20.06 | 10.21 | 5.71 | 7.31 | 18.5 | 0.86 | 0.85 | 0.000 |
| | 8 | Intermediate | 1.0 | 1.0 | 8.05 | 6.24 | 6.46 | 5.05 | 10.1 | 0.93 | 0.93 | 0.003 |
| | 8 | Dissipation | 0.9 | 0.9 | 5.85 | 8.04 | 6.88 | 9.95 | 24.1 | 1.00 | 0.99 | 0.936 |
| | 3 | Formation | 2.2 | 2.1 | 30.26 | 15.23 | 8.86 | 12.93 | 27.7 | 0.86 | 0.87 | 0.057 |
| | 3 | Intermediate | 1.6 | 1.5 | 5.58 | 5.66 | 5.50 | 3.83 | 6.8 | 1.10 | 1.10 | 0.000 |
| | 3 | Dissipation | 3.7 | 3.7 | 9.01 | 14.02 | 9.40 | 1.97 | 9.9 | 1.06 | 1.07 | 0.035 |
| | 5 | Formation | 1.4 | 1.4 | 9.40 | 4.93 | 5.01 | 1.80 | 22.8 | 0.94 | 0.94 | 0.268 |
| Mid | 5 | Intermediate | 1.1 | 1.1 | 8.44 | 2.95 | 4.74 | 0.99 | 8.3 | 1.01 | 1.01 | 0.491 |
| | 5 | Dissipation | 1.9 | 1.8 | 31.10 | 4.80 | 9.52 | 3.64 | 35.8 | 1.07 | 1.08 | 0.471 |
| | 8 | Formation | 1.1 | 1.0 | 41.14 | 12.56 | 4.21 | 3.75 | 28.6 | 0.87 | 0.85 | 0.038 |
| | 8 | Intermediate | 1.0 | 1.0 | 8.54 | 7.60 | 4.97 | 1.66 | 8.9 | 0.94 | 0.94 | 0.006 |
| | 8 | Dissipation | 0.9 | 0.9 | 16.03 | 6.14 | 6.72 | 1.82 | 11.8 | 1.00 | 1.00 | 0.957 |
| | 3 | Formation | 1.9 | 1.9 | 20.17 | 14.24 | 5.18 | 3.85 | 18.3 | 0.82 | 0.83 | 0.002 |
| | 3 | Intermediate | 1.5 | 1.5 | 6.28 | 6.16 | 3.82 | 4.13 | 7.5 | 1.05 | 1.04 | 0.009 |
| | 3 | Dissipation | 3.5 | 3.4 | 10.70 | 6.53 | 4.76 | 2.37 | 10.9 | 1.00 | 1.01 | 0.952 |
| | 5 | Formation | 1.4 | 1.4 | 15.44 | 9.89 | 5.85 | 2.23 | 13.6 | 0.86 | 0.87 | 0.002 |
| End | 5 | Intermediate | 1.1 | 1.1 | 6.05 | 4.66 | 4.94 | 1.13 | 6.1 | 0.98 | 0.98 | 0.152 |
| | 5 | Dissipation | 1.6 | 1.5 | 35.08 | 7.39 | 9.54 | 17.71 | 39.6 | 0.84 | 0.84 | 0.090 |
| | 8 | Formation | 1.1 | 1.1 | 18.14 | 8.38 | 21.99 | 7.37 | 20.7 | 0.84 | 0.84 | 0.001 |
| | 8 | Intermediate | 0.99 | 0.98 | 10.88 | 6.37 | 4.42 | 4.83 | 11.29 | 0.86 | 0.87 | 0.00 |
| | 8 | Dissipation | 0.86 | 0.86 | 10.54 | 6.56 | 4.25 | 6.91 | 12.64 | 0.64 | 0.70 | 0.00 |

**Table 21: Droplet Size Distribution (SPAN) - Reference Product**

| Life Stage | Dist. (cm) | Plume Stage | Arith Mean | Geo Mean | Within Lot %CV | | | Between Lot %CV | Total %CV |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CF6681A | CM6923A | DB7018A | | |
| | 3 | Formation | 2.6 | 2.5 | 17.76 | 27.42 | 39.18 | 5.12 | 28.38 |
| | 3 | Intermediate | 1.4 | 1.4 | 3.66 | 4.91 | 5.04 | 2.09 | 4.73 |
| | 3 | Dissipation | 3.1 | 3.0 | 14.69 | 22.24 | 21.98 | 8.76 | 20.88 |
| | 5 | Formation | 1.5 | 1.5 | 24.70 | 19.94 | 18.60 | 6.93 | 21.60 |
| Beg | 5 | Intermediate | 1.1 | 1.1 | 5.59 | 4.59 | 5.19 | 1.21 | 5.07 |
| | 5 | Dissipation | 2.3 | 2.2 | 25.46 | 39.30 | 20.65 | 9.92 | 28.57 |
| | 8 | Formation | 1.2 | 1.2 | 14.94 | 7.35 | 6.55 | 2.24 | 10.00 |
| | 8 | Intermediate | 1.1 | 1.1 | 9.21 | 6.12 | 6.78 | 5.04 | 8.26 |
| | 8 | Dissipation | 0.9 | 0.9 | 11.27 | 6.83 | 12.69 | 3.59 | 10.74 |
| | 3 | Formation | 2.5 | 2.4 | 28.49 | 29.65 | 37.58 | 9.71 | 32.37 |
| | 3 | Intermediate | 1.4 | 1.4 | 5.29 | 4.70 | 5.97 | 2.33 | 5.52 |
| | 3 | Dissipation | 3.5 | 3.5 | 14.48 | 10.09 | 12.18 | 4.15 | 12.33 |
| | 5 | Formation | 1.5 | 1.5 | 22.78 | 18.00 | 7.76 | 6.38 | 18.08 |
| Mid | 5 | Intermediate | 1.1 | 1.1 | 5.16 | 4.29 | 3.94 | 0.97 | 4.41 |
| | 5 | Dissipation | 1.8 | 1.7 | 44.76 | 27.03 | 32.20 | 20.58 | 38.73 |
| | 8 | Formation | 1.24 | 1.22 | 36.64 | 7.86 | 12.86 | 8.46 | 24.41 |
| | 8 | Intermediate | 1.05 | 1.05 | 8.45 | 5.56 | 7.62 | 3.07 | 7.52 |
| | 8 | Dissipation | 0.89 | 0.88 | 9.63 | 8.31 | 9.55 | 3.42 | 9.32 |
| | 3 | Formation | 2.3 | 2.2 | 24.33 | 34.71 | 19.64 | 6.98 | 27.32 |
| | 3 | Intermediate | 1.4 | 1.4 | 4.82 | 5.85 | 3.66 | 2.02 | 4.97 |
| | 3 | Dissipation | 3.5 | 3.4 | 10.56 | 12.87 | 17.71 | 2.52 | 13.60 |
| | 5 | Formation | 1.6 | 1.6 | 18.68 | 26.78 | 9.75 | 8.16 | 20.64 |
| End | 5 | Intermediate | 1.1 | 1.1 | 4.85 | 6.16 | 4.21 | 1.90 | 5.18 |
| | 5 | Dissipation | 1.9 | 1.8 | 48.16 | 33.76 | 18.56 | 27.60 | 38.73 |
| | 8 | Formation | 1.30 | 1.28 | 17.44 | 24.30 | 12.24 | 7.95 | 19.15 |
| | 8 | Intermediate | 1.14 | 1.13 | 12.75 | 11.45 | 29.60 | 6.69 | 20.55 |
| | 8 | Dissipation | 1.35 | 1.22 | 49.97 | 49.34 | 47.23 | 16.43 | 49.19 |

**Table 22: Plume Duration for Beginning of Product Life - Spray #5**

| Product | Distance (cm) | Plume Section | Duration (msec) Mean | %CV | Min | Max | T / R |
|---|---|---|---|---|---|---|---|
| TEST | 3 | Int | 80.8 | 12.4 | | | 0.792 |
| | | Entire | 145.2 | 16.0 | | | 0.966 |
| | 5 | Int | 78.5 | 12.1 | | | 0.791 |
| | | Entire | 187.3 | 14.6 | | | 1.030 |
| | 8 | Int | 70.9 | 12.6 | | | 0.821 |
| | | Entire | 243.1 | 18.9 | | | 0.997 |
| REF | 3 | Int | 102.0 | 11.4 | | | |
| | | Entire | 150.3 | 8.5 | | | |
| | 5 | Int | 99.3 | 12.0 | | | |
| | | Entire | 181.9 | 11.9 | | | |
| | 8 | Int | 86.4 | 15.2 | | | |
| | | Entire | 243.7 | 22.7 | | | |

**Table 23: Plume Duration for End of Product Life -Spray #54**

| Product | Distance (cm) | Plume Section | Duration (msec) Mean | %CV | Min | Max | T / R |
|---|---|---|---|---|---|---|---|
| TEST | 3 | Int | 90.3 | 21.4 | | | 0.796 |
| | | Entire | 158.4 | 17.9 | | | 0.959 |
| | 5 | Int | 82.8 | 14.6 | | | 0.795 |
| | | Entire | 212.3 | 25.6 | | | 0.983 |
| | 8 | Int | 62.1 | 29.6 | | | 0.698 |
| | | Entire | 240.9 | 24.8 | | | 1.007 |
| REF | 3 | Int | 113.3 | 7.8 | | | |
| | | Entire | 165.2 | 15.0 | | | |
| | 5 | Int | 104.1 | 11.5 | | | |
| | | Entire | 215.9 | 20.8 | | | |
| | 8 | Int | 89.1 | 14.8 | | | |
| | | Entire | 239.2 | 16.3 | | | |

### 4. Drug in Small Particles / Droplets by Cascade Impactor

No Additional Data.

### 5. Particle / Droplet Size Distribution by Cascade Impactor

Not Applicable to this Product.

### 6. Drug Particle Size Distribution by Microscopy

Not Applicable to this Product.

### 7. Spray Pattern

**Table 24: Spray Pattern Metrics - Test Data**

| Life Stage | Dist. (cm) | Metric | Arith. Mean | Geo Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T/R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BEG | 3 | Dmax | 40.38 | 40.09 | 9.35 | 12.52 | 15.66 | 1.14 | 12.33 | 0.978 | 0.481 |
| | | Dmin | 31.87 | 31.62 | 8.75 | 10.75 | 17.79 | 3.53 | 13.09 | 1.006 | 0.824 |
| | | Ovality | 1.27 | 1.27 | 6.72 | 7.73 | 4.17 | 3.51 | 6.88 | 0.972 | 0.143 |
| | 4 | Dmax | 53.45 | 52.86 | 12.10 | 12.94 | 19.05 | 6.04 | 15.59 | 1.115 | 0.026 |
| | | Dmin | 39.68 | 39.16 | 10.92 | 11.54 | 21.46 | 9.00 | 16.97 | 1.129 | 0.008 |
| | | Ovality | 1.36 | 1.35 | 4.97 | 10.64 | 9.54 | 5.13 | 9.61 | 0.988 | 0.620 |
| | 5 | Dmax | 71.45 | 70.67 | 14.58 | 17.36 | 13.88 | 2.83 | 14.93 | 1.178 | 0.000 |
| | | Dmin | 48.73 | 48.14 | 8.77 | 15.70 | 19.46 | 5.88 | 15.58 | 1.219 | 0.000 |
| | | Ovality | 1.48 | 1.47 | 11.97 | 16.68 | 10.36 | 3.36 | 13.25 | 0.966 | 0.324 |
| END | 3 | Dmax | 43.16 | 42.71 | 8.02 | 9.71 | 21.11 | 7.14 | 15.53 | 1.182 | 0.000 |
| | | Dmin | 33.49 | 33.02 | 13.04 | 13.34 | 18.82 | 9.78 | 17.22 | 1.212 | 0.000 |
| | | Ovality | 1.30 | 1.29 | 10.40 | 10.97 | 6.90 | 3.38 | 9.74 | 0.975 | 0.338 |
| | 4 | Dmax | 61.00 | 60.42 | 6.90 | 11.36 | 15.67 | 10.34 | 14.75 | 1.348 | 0.000 |
| | | Dmin | 47.34 | 46.82 | 7.72 | 11.28 | 16.94 | 10.76 | 15.57 | 1.406 | 0.000 |
| | | Ovality | 1.29 | 1.29 | 7.33 | 6.51 | 8.28 | 1.69 | 7.28 | 0.959 | 0.063 |
| | 5 | Dmax | 82.66 | 82.03 | 6.24 | 14.55 | 14.36 | 4.57 | 12.29 | 1.385 | 0.000 |
| | | Dmin | 59.37 | 58.92 | 8.71 | 13.50 | 13.13 | 5.23 | 12.24 | 1.527 | 0.000 |
| | | Ovality | 1.40 | 1.39 | 6.96 | 6.45 | 10.92 | 1.87 | 8.15 | 0.907 | 0.002 |

**Table 25: Spray pattern Metrics - Reference Data**

| Life Stage | Dist. (cm) | Metric | Arith. Mean | Geo Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% |
|---|---|---|---|---|---|---|---|---|---|
| BEG | 3 | Dmax | 41.24 | 41.01 | 11.33 | 10.37 | 11.52 | 0.95 | 10.72 |
| | | Dmin | 31.65 | 31.44 | 9.89 | 11.76 | 11.43 | 5.11 | 11.49 |
| | | Ovality | 1.31 | 1.30 | 6.48 | 5.96 | 9.64 | 4.43 | 8.26 |
| | 4 | Dmax | 48.20 | 47.39 | 21.89 | 19.33 | 18.58 | 4.47 | 19.60 |
| | | Dmin | 35.15 | 34.69 | 15.82 | 20.01 | 14.99 | 5.94 | 17.41 |
| | | Ovality | 1.37 | 1.37 | 9.89 | 8.69 | 14.24 | 4.42 | 11.56 |
| | 5 | Dmax | 60.84 | 60.00 | 10.86 | 17.70 | 17.35 | 9.42 | 17.22 |
| | | Dmin | 40.15 | 39.50 | 9.61 | 21.05 | 17.51 | 11.38 | 19.22 |
| | | Ovality | 1.53 | 1.52 | 9.64 | 10.35 | 17.07 | 3.15 | 12.80 |
| END | 3 | Dmax | 36.49 | 36.15 | 12.82 | 15.00 | 13.14 | 5.18 | 13.97 |
| | | Dmin | 27.53 | 27.24 | 9.38 | 15.18 | 16.73 | 7.69 | 15.18 |
| | | Ovality | 1.34 | 1.33 | 8.15 | 7.15 | 17.78 | 2.79 | 11.97 |
| | 4 | Dmax | 45.36 | 44.81 | 14.21 | 15.37 | 18.97 | 4.64 | 16.17 |
| | | Dmin | 33.58 | 33.29 | 12.74 | 14.54 | 12.22 | 4.23 | 13.29 |
| | | Ovality | 1.35 | 1.35 | 9.64 | 6.66 | 14.95 | 0.41 | 10.56 |
| | 5 | Dmax | 60.30 | 59.24 | 19.45 | 14.83 | 21.52 | 6.31 | 18.69 |
| | | Dmin | 39.03 | 38.58 | 11.39 | 15.47 | 16.77 | 7.42 | 15.57 |
| | | Ovality | 1.55 | 1.54 | 13.64 | 14.59 | 17.69 | 2.01 | 15.01 |

## 8. Plume Geometry

**Table 26: Plume Angle Data - 90° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 82.0 | 0.81 | 3.32 | 1.43 | 0.76 | 2.17 | 1.007 | 0.0785 |
| | Formation | 91.6 | 0.87 | 2.06 | 0.73 | 0.16 | 1.32 | 0.997 | 0.3717 |
| | Dissipation | 68.9 | 1.52 | 1.73 | 1.68 | 0.71 | 1.69 | 0.993 | 0.0911 |
| REF | Initiation | 81.4 | 0.82 | 0.48 | 0.78 | 0.07 | 0.69 | | |
| | Formation | 92.0 | 0.65 | 2.82 | 0.84 | 0.17 | 1.69 | | |
| | Dissipation | 69.4 | 1.67 | 0.97 | 1.93 | 0.72 | 1.63 | | |

**Table 27: Plume Height Data - 90° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 49.3 | 14.68 | 14.86 | 10.55 | 2.33 | 13.15 | 1.184 | 0.000 |
| | Formation | 134.7 | 3.60 | 2.06 | 0.73 | 1.75 | 3.20 | 1.006 | 0.481 |
| REF | Initiation | 41.5 | 9.08 | 11.09 | 10.97 | 4.06 | 10.57 | | |
| | Formation | 133.9 | 2.94 | 3.91 | 3.63 | 0.30 | 3.40 | | |

**Table 28: Plume Width Data - 90° Plume Angle View**

| | Plume Sector | Mean | Within Lot CV% Lot 1 | Lot 2 | Lot 3 | Between Lot CV% | Total CV% | T / R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|
| TEST | Initiation | 32.2 | 10.97 | 14.23 | 9.51 | 2.01 | 11.39 | 1.103 | 0.0002 |
| | Formation | 88.6 | 2.15 | 6.22 | 2.88 | 1.76 | 4.30 | 1.015 | 0.1093 |
| REF | Initiation | 28.83 | 8.48 | 7.10 | 6.49 | 0.73 | 7.17 | | |
| | Formation | 87.32 | 2.49 | 2.90 | 3.45 | 0.35 | 2.88 | | |

## B. Formulation Data

**Table 29: Test and Reference Formulations**

| | Novex Pharma Desmopressin Acetate Nasal Spray | | Aventis DDAVP® Nasal Spray | |
|---|---|---|---|---|
| Ingredient | Per spray (0.1 mL) | Per mL | Per spray (0.1 mL) | Per mL |
| Desmopressin Acetate | 0.01mg | 0.1mg | 0.01 mg | 0.1mg |
| Benzalkonium Chloride, NF 50% w/w | 0.02 mg | 0.2 mg | 0.02 mg | 0.2 mg |
| Citric Acid, USP (Monohydrate) | 0.17 mg | 1.7 mg | 0.17 mg | 1.7 mg |
| Purified Water, USP | q.s. | q.s. | q.s. | q.s. |
| Sodium Chloride, USP | 0.75 mg | 7.5 mg | 0.75 mg | 7.5 mg |
| Disodium Phosphate Dihydrate | -- | -- | 0.30 mg | 3.0 mg |
| Sodium Phosphate Dibasic Heptahydrate USP | 0.452 mg | 4.52 mg | -- | -- |

The firm's and innovator's formulations are identical except composition of dibasic sodium phosphate. The firm utilized the heptahydrate while the innovator used the dihydrate form. The difference in the weight of dibasic sodium phosphate between the test and reference products is due to the degree of hydration. See Table 30 below.

**Table 30: Sodium Phosphate Comparison**

| | Moles of $H_2O$ | MW | Amount Used | Weight of $H_2O$ | Amount of $Na_2PO_4$ |
|---|---|---|---|---|---|
| Dibasic Sodium Phosphate anhydrous | 0 | 141.96 | 0 | -- | -- |
| Dibasic Sodium Phosphate dihydrate | 2 | 177.99 | 3.00 mg | 0.60 mg | 2.40 mg |
| Dibasic Sodium Phosphate heptahydrate | 7 | 268.07 | 4.52 mg | 2.12 mg | 2.40 mg |
| Water | -- | 18.016 | -- | -- | -- |

## C. Consult Reviews

None.

## D. Additional Attachments

**Population Bioequivalence Analysis Data Files**

| STUDY | OUTPUT |
|---|---|
| **pBE Analysis 3mm distance** | span_dist3.doc |
| **pBE Analysis 5mm distance** | span_dist5.doc |
| **pBE Analysis 8mm distance** | span_dist8.doc |

Reviewer Note: pBE analysis provided by Devrat Patel, Pharm.D.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-703 APPLICANT: Novex Pharma

DRUG PRODUCT: Desmopressin Acetate Nasal Spray 0.01mg/spray

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

You did not provide an expiration date for the test lot. Please provide an expiration date for the test lot# 2X130.

The three Spray Pattern distances from the actuator orifice submitted were not at least 3cm apart. Please perform spray pattern testing at 2 distances from the actuator orifice, within the range of 3cm to 7cm, that are at least 3cm apart. You can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for bioequivalence evaluation. Alternatively, you can use automated analysis of the pattern area and ovality ratios of the test and reference products at the beginning of life stage for bioequivalence evaluation.

Sincerely yours,

Barbara M Davit

for

Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CC: ANDA 76-703
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-652/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

v:\firmsnz\novex\ltrs&rev\76703N0303.doc

Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 4/27/04
HFD-652/ S.G. Nerurkar 5/28/04
HFD-650/ D.P. Conner 5/28/04

BIOEQUIVALENCY - INCOMPLETE Submission date: 26 March 2003

| | | | |
|---|---|---|---|
| 1. | Other (STS) | Strengths: | 0.01% |
| | | Outcome: | IC |
| 2. | Other (STS) | Strengths: | 0.01% |
| | | Outcome: | IC |
| 3. | Other (STS) | Strengths: | 0.01% |
| | | Outcome: | IC |
| 4. | Other (STS) | Strengths: | 0.01% |
| | | Outcome: | IC |

Outcome Decisions: IC - Incomplete

# DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

| | |
|---|---|
| **ANDA No.** | 76-703 |
| **Drug Product Name** | Desmopressin Acetate Nasal Spray, 0.01mg/spray |
| **Strength** | 0.01mg/spray (0.01% solution) |
| **Applicant Name** | Novex Pharma |
| **Address** | 380 Elgin Mills Rd East<br>Richmond Hill, Ontario, Canada L4C 5H2 |
| **Submission Date(s)** | 26 March 2003 |
| **Amendment Date(s)** | 04 August 2004 |
| **Reviewer** | James L. Osterhout |
| **First Generic** | No |
| **File Location** | V:\firmsnz\novex\ltrs&rev\76703A0804 |

## I. Executive Summary

In the original submission the firm provided the following in-vitro tests: i) single actuation content through container life, ii) priming and re-priming, iii) droplet size distribution by laser diffraction, iv) droplet size distribution by cascade impactor, v) spray pattern, and vi) plume geometry. Of these six, the DBE deemed that only the spray pattern test was incomplete. The amendment contains new spray pattern data in support of a request for waiver of in-vivo bioavailability requirements for Desmopressin Acetate Nasal Spray 0.01mg/spray (Nasal Solution 0.01%) 5mL bottle under 21 CFR 320.22(b)(3). The reference listed drug (RLD) is DDAVP® Nasal Spray (desmopressin acetate), available in a 5mL bottle with spray pump that delivers 10μg per actuation, from Aventis Pharmaceutical Incorporated (NDA 17-922-003).

In this amendment, the firm submitted manual analysis of spray patterns for the test and reference products using chromographic imaging of the spray pattern on TLC plates[1]. The ratios of the test geometric means to the reference geometric means for the Dmax and ovality metric were within the 0.9-1.11 acceptance range for beginning of product life actuations (spray #5). Therefore, the spray pattern data is acceptable.

The application is acceptable.

---

[1] The firm submitted spray pattern data obtained by [redacted] on 08 July 2004. The firm subsequently withdrew the study on 29 July 2004 (See Table 2 and Comments on Spray Pattern: Page 6).

## II. Table of Contents



## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Desmopressin Acetate Nasal Solution (Nasal Spray) 0.01% |
| **Reference Product** | DDAVP® Nasal Spray 0.01mg / spray (needs no refrigeration) |
| **RLD Manufacturer** | Aventis Pharmaceuticals Inc. |
| **NDA No.** | N017922 (003 product) |
| **RLD Approval Date** | 07 August 1996 |
| **Indication** | Desmopressin Acetate Nasal Spray is indicated for the 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. |

### B. Contents of Submission

| Studies | Y/N |
|---|---|
| **Single Actuation Content Through Container Life** | No |
| **Priming and Re-priming** | No |
| **Droplet Size Distribution by Laser Diffraction** | No |
| **Drug in Small Particles / Droplets by Cascade Impactor** | No |
| **Particle / Droplet Size Distribution by Cascade Impactor (aerosol only)** | No |
| **Drug Particle Size Distribution by Microscopy (suspension only)** | No |
| **Spray Pattern** | Yes |
| **Plume Geometry** | No |

### C. Waiver Request(s) For Other Strength

| | |
|---|---|
| **Strengths for which waivers requested** | None |
| **Regulation cited** | Not Applicable |
| **Test and reference are Q1 & Q2?** | Not Applicable |
| **Dissolution is acceptable?** | Not Applicable |
| **Waiver granted?** | Not Applicable |

### D. Container and Closure Systems

#### 1. Actuator & Pump Information

| | Test | Reference |
|---|---|---|
| **Supplier** | [redacted] | [redacted] |
| **Pump Description** | A white plastic metering spray pump with a clear plastic protection cap. The pump is fitted with a white nasal spray actuator. | A white plastic metering spray pump with a clear plastic protection cap. The pump is fitted with a white nasal spray actuator. |
| **Actuator Metrics** | | |
| **Height (mm)** | 35.00 mm | 34.13 mm |
| **Outer width (mm)** | 4.27 mm | 6.15 mm |
| **Inner width (mm)** | 1.73 mm | 3.10 mm |
| **Orifice diameter (um)** | 251.42 um | 282.50 um |
| **Dip Tube Length (mm)** | 35.12 mm | 49.31 mm |
| **Lot #1** | GC7300 | NA |
| **Lot #2** | GC7301 | NA |
| **Lot #3** | GC7302 | NA |

#### 2. Container Information

The innovator product actuators are crimped onto a 5mL flat bottom glass container. The firm indicated that their actuator screws onto their container, which is a 5mL V-bottom glass container.

### E. Procedures and Information Applicable to All Tests

| Summary | |
|---|---|
| **Study No.** | Not Given |
| **Study Site(s)** | Novex Pharma<br>380 Elgin Mills Road East<br>Richmond Hill, Ontario, Canada L4C 5H2 |

| | |
|---|---|
| **Study Dates** | Not Given |
| **Number of Units Tested / Lot** | 10 |
| **Strength Tested** | 0.01mg/spray (50 doses of 10µg, 5mL bottle) |

| | | |
|---|---|---|
| **Test Lot #'s (expiration date)** | **Lot#** | 2X130 (manufactured on 15 May 2002) |
| | **Lot Size** | [redacted] |
| | **Sub-Lot #** | GC7300 actuator |
| | | GC7301 actuator |
| | | GC7302 actuator |
| | **Units Tested / Lot** | 10 |
| **Reference Lot #'s (expiration date)** | **Lot #1** | EF77774B (June 2005) |
| | **Lot #2** | EL8028A (Nov 2004) |
| | **Lot #3** | EL8028B (Nov 2004) |
| | **Units Tested / Lot** | 10 |

| | |
|---|---|
| **Actuation method** | [redacted] Automated Spray Pump Actuation |
| **SOP's submitted (Y/N)** | Yes (GM-143) Volume 1.1, pages 126-143 |
| **Dose time (msec)** | 20 ± 2 |
| **Return time (msec)** | 30 ± 5 |
| **Hold time (sec)** | 0.5 |
| **Actuation force (kg)** | 6.0 ± 0.5 |

Reviewer Note: The lot numbers used for the spray pattern data in the amendment are different from those used in the original application. The firm did not submit the expiration dates for these lots in the amendment. The firm was notified of this deficiency in a phone teleconference, and submitted this data to the DBE via fax. This is acceptable.

## F. In-Vitro Studies

### 1. Spray Pattern

| Study Summary | |
|---|---|
| **Method Description** | photo image of a TLC plate cross-section of the spray, visualized with a chromatographic agent specific for the drug product |
| **Visualization Apparatus** | Not Applicable |
| **Actuation Apparatus** | ——— |
| **Spray Pattern Distance 1** | 3 cm |
| **Spray Pattern Distance 2** | 6 cm |
| **20% of Spray Pattern Images Provided?** | YES |
| **If so, picture or digital file?** | picture |
| **Metrics Determined by Software?** | no, manual |

| | |
|---|---|
| **Method** | pp 9-14 of 04 Aug 2004 submission |
| **Validation** | Not Applicable |
| **Method Acceptable?** | Yes |

The firm submitted spray pattern data at two distances from the actuator tip (3cm and 6cm) to determine the maximum diameter (Dmax), minimum diameter (Dmin), and the ovality ratio (Dmax/Dmin). The firm provided 20% of the TLC plate pictures with the metrics indicated on the spray patterns in the application.

**Table 1: Spray Pattern Dmax, Dmin, and Ovality - Test and Reference Data**

| | Dist. | | Arith. | Geo | Within Lot CV% | | | Between | Total | T/R Geo | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | (cm) | Metric | Mean | Mean | Lot 1 | Lot 2 | Lot 3 | Lot CV% | CV% | Mean | Value |
| TEST | 3 | Dmax | 5.59 | 5.58 | 7.58 | 6.33 | 7.21 | 1.64 | 6.94 | 0.925 | 0.000 |
| | | Dmin | 4.77 | 4.76 | 10.36 | 8.58 | 6.89 | 1.95 | 8.58 | 0.887 | 0.000 |
| | | Ovality | 1.18 | 1.17 | 7.21 | 5.81 | 4.22 | 1.25 | 5.79 | 1.042 | 0.023 |
| | 6 | Dmax | 9.55 | 9.53 | 6.10 | 5.12 | 7.35 | 2.57 | 6.38 | 1.075 | 0.000 |
| | | Dmin | 7.36 | 7.30 | 15.74 | 12.75 | 10.45 | 4.58 | 13.21 | 1.160 | 0.000 |
| | | Ovality | 1.31 | 1.30 | 17.21 | 12.70 | 6.59 | 2.85 | 12.83 | 0.926 | 0.039 |
| REF | 3 | Dmax | 6.04 | 6.03 | 5.74 | 6.14 | 7.01 | 2.97 | 6.57 | | |
| | | Dmin | 5.38 | 5.36 | 4.89 | 11.11 | 5.65 | 0.39 | 7.48 | | |
| | | Ovality | 1.13 | 1.13 | 5.13 | 9.29 | 6.90 | 2.95 | 7.54 | | |
| | 6 | Dmax | 8.89 | 8.86 | 7.77 | 11.02 | 5.01 | 2.16 | 8.23 | | |
| | | Dmin | 6.36 | 6.29 | 19.05 | 12.15 | 9.46 | 2.92 | 13.97 | | |
| | | Ovality | 1.43 | 1.41 | 23.50 | 11.61 | 10.94 | 3.16 | 16.20 | | |

**Comments on Spray Pattern:**

Unlike the original submission, the spray pattern distances in this amendment were at least 3 cm apart as specified in the FDA guidance. The ratios of the test geometric means to the reference geometric means for the Dmax and ovality metric were within the 0.9-1.11 acceptance range for beginning (spray #5) of product life actuations. The ratios of the test geometric means to the reference geometric means for the Dmin metrics were not within the 0.9-1.11 acceptance range for the beginning of product life. This failure is of no consequence since only the Ovality ratio and Dmax need to be evaluated as per the FDA guidance. The data are acceptable.

In the 20% of the spray pattern TLC plate photos submitted, none of the Dmax vector lines cross the spray pattern boundary. Un-weighted center of mass values were obtained by manual drawing of the Dmax and Dmin vector lines. All of the spray pattern outline boundaries were acceptable and generally corresponded to the drawn circular boundary. The Dmax and Dmin values analyzed in this review were calculated from the outline boundaries (true shape).

Additionally, the firm submitted spray pattern data obtained by [redacted] on 08 July 2004, then withdrew the study on 29 July 2004. When this data was reviewed for BE determination, the area metric passed the BE criteria. Therefore, the spray pattern data obtained from the [redacted] resulted in an acceptable study (see Table 2: Withdrawn Spray Pattern Data - [redacted], Page 6). This finding supports the acceptable data obtained by manual analysis in this submission.

The firm did not provide the expiration dates for the reference products lots used in this amendment (the reference lots used in this submission were different from those used in the original application).

UPDATE: The firm provided the expiration dates for the reference lots via fax following a teleconference with A. Sigler on 26 October 2004.

The spray pattern data is acceptable.

**G. Deficiency Comments**

None

**H. Recommendations**

The in-vitro performance data submitted by Novex Pharma on the test product Desmopressin Acetate Nasal Solution (Nasal Spray) 0.01% Lot #2X130, comparing it with the RLD product, Aventis Pharmaceutical's DDAVP® Nasal Spray has been found acceptable by the Division of Bioequivalence.

05 NOV 2004

James Osterhout, Reviewer, Branch I — Date

11/5/2004

Shriniwas G. Nerurkar, Team Leader, Branch I — Date

for Barbara M. Davit 11/6/04

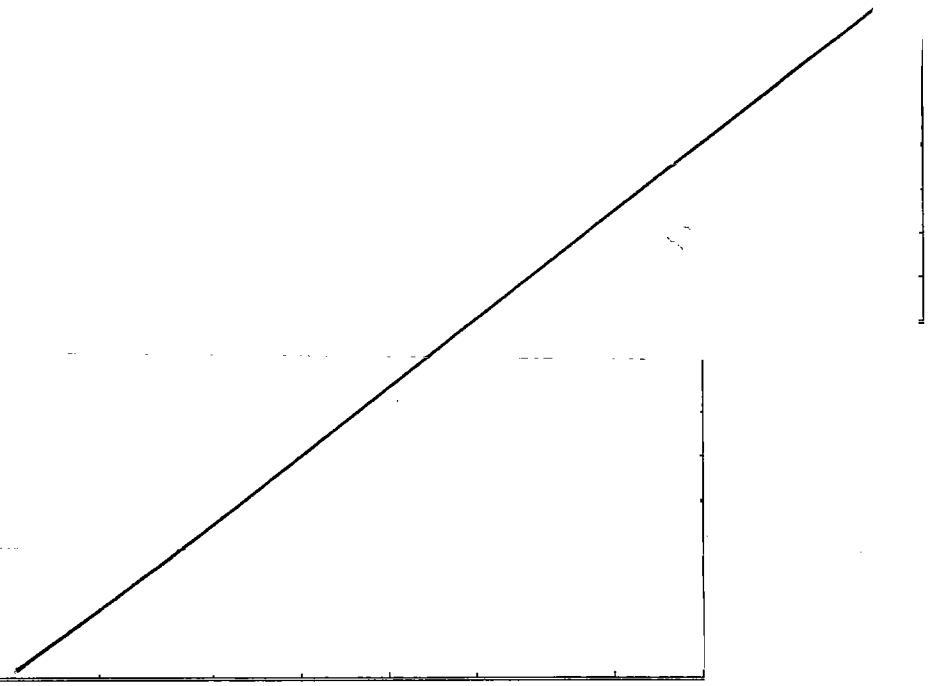
Dale P. Conner, Pharm. D. — Date
Director, Division of Bioequivalence
Office of Generic Drugs

## IV. Appendix

### I. Additional Attachments

**Table 2: Withdrawn Spray Pattern Data -** _____

| | Dist. (cm) | Metric | Arith. Mean | Geo Mean | Within Lot CV% Lot 1 | Within Lot CV% Lot 2 | Within Lot CV% Lot 3 | Between Lot CV% | Total CV% | T/R Geo Mean | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TEST | 3 | Dmax | | | | | | | | | |
| | | Dmin | | | | | | | | | |
| | | Ovality | | | | | | | | | |
| | | Area | | | | | | | | | |
| | 6 | Dmax | | | | | | | | | |
| | | Dmin | | | | | | | | | |
| | | Ovality | | | | | | | | | |
| | | Area | | | | | | | | | |
| REF | 3 | Dmax | | | | | | | | | |
| | | Dmin | | | | | | | | | |
| | | Ovality | | | | | | | | | |
| | | Area | | | | | | | | | |
| | 6 | Dmax | | | | | | | | | |
| | | Dmin | | | | | | | | | |
| | | Ovality | | | | | | | | | |
| | | Area | | | | | | | | | |



APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-703 APPLICANT: Novex Pharma

DRUG PRODUCT: Desmopressin Acetate Nasal Spray 0.01mg/spray

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

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CC: ANDA 76-703
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-652/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

v:\firmsnz\novex\ltrs&rev\76703A0804.doc

Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 05 NOV 2004
HFD-655/ G.J.P. Singh 11-5-04
HFD-652/ S.G. Nerurkar
HFD-650/ D.P. Conner 11/6/04

11/8/04

BIOEQUIVALENCE-ACCEPTABLE Submission Date: 26 March 2003
Amendment Date: 04 August 2004

1. Other (STS) Strengths: 0.01%
Outcome: AC

Outcome Decisions: AC - Acceptable

**OFFICE OF GENERIC DRUGS**
**DIVISION OF BIOEQUIVALENCE**

| | |
|---|---|
| **ANDA #:** | 76-703 **SPONSOR:** Novex Pharma |
| **DRUG & DOSAGE FORM:** | Desmopressin Acetate Nasal Spray |
| **STRENGTH(S):** | 0.01mg/spray |
| **TYPES OF STUDIES:** | In Vitro Bioequivalence Studies for Nasal Sprays |
| **CLINICAL STUDY SITE(S):** | Not Applicable |
| **ANALYTICAL SITE(S):** | Novex Pharma<br>Richmond Hill, Ontario, Canada |

| | |
|---|---|
| **STUDY SUMMARY:** | The in-vitro studies are acceptable. (See review) |
| **DISSOLUTION:** | Not Applicable |

**DSI INSPECTION STATUS**

| Inspection needed: | | **Inspection status:** | **Inspection results:** |
|---|---|---|---|
| First Generic | | | |
| New facility | | | |
| For cause | | | |
| Other | | | |

N/A

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes ☐ No ☐ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm?
Yes ☐ No ☐

**PROJECT MANAGER:** _____ **DATE:** _____

**PRIMARY REVIEWER:** James L. Osterhout, PhD **BRANCH:** I
**INITIAL:** _____ **DATE:** 05 NOV 2004

**TEAM LEADER:** Shriniwas G. Nerurkar, PhD **BRANCH:** I
**INITIAL:** _____ **DATE:** 11/5/2004

**DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Dale P. Conner, Pharm.D.
**INITIAL:** _____ **DATE:** 11/6/04

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# ADMINISTRATIVE DOCUMENTS

## OGD APPROVAL ROUTING SUMMARY

ANDA # 76-703 Applicant Novex Pharma
Drug Desmopressin Acetate Nasal Solution Strength(s) 0.01%

**APPROVAL** ☐ **TENTATIVE APPROVAL** ☑ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

**REVIEWER:** **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 15 Nov 2004 Initials MMS
Date 11/30/04 Initials for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# 17-922
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked 11/30/04
If Para. IV Certification- did applicant
Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☑ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐ (Not Yet determined)
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: PIV to 931, 931, 850 & 407, sued w/in 45 days on 931
Comments:
30 month = 11/15/2006 eligible for TA only

2. Project Manager, ~~Peter Chen~~ Team 2
Review Support Branch
Date 11/10/04 Initials PC
Date 11/24/04 Initials PC

Original Rec'd date 3/26/03 4/1/03
Date Acceptable for Filing ~~3/26/03~~ 4/1/03
Patent Certification (type) IV
Date Patent/Exclus.expires
EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 2/4/04
Date of Office Bio Review 11/6/04
Date of Labeling Approv. Sum 9/21/04
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
First Generic Yes ☐ No ☑
Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)**
OGD Regulatory Counsel,
Pre-MMA Language included ☑
Post-MMA Language Included ☐
Comments: see revised version
Date 11/24/04 Initials DTR

4. Div. Dir./~~Deputy Dir.~~
Chemistry Div. I ~~II OR~~ III
Comments:
Date 11/29/04 Initials DRS

The CMC section is satisfactory for TA

**REVIEWER:** **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. ~~Multiple~~ One ANDA has been approved for this drug product. (ANDA 74-830/Bausch+Lomb). It is for a refrigerated drug product).

6. Vacant RLD-DDAVP Nasal Spray 0.01mg/spray Date_____
Deputy Dir., DLPS NDA 17-922 Initials_____
Aventis Pharmaceutical Products, Inc. (003)

7. Peter Rickman Date 11/30/04
Director, DLPS Initials for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 2/4/04 verified 11/30/04. NO AI. Labels noted. Bioequivalence studies (in vitro) found acceptable 11/5/04. Drug product is "RX" to the RLD, office-level biowaiver issued 11/6/04. Labeling found acceptable for TA 9/14/04. CMC found acceptable 11/29/04 OR Methods validation was completed and found acceptable. Micro-N/A.

8. Robert L. West Date 11/30/2004
Deputy Director, OGD Initials for
Para.IV Patent Cert: Yes X No ☐; Pending Legal Action: Yes X No ☐; Petition: Yes ☐ No ☐
Comments: Novex made paragraph IV certifications to the '931, '413, '850, and '407 patents. Novex was sued within the 45-day period only on the '931 patent. Litigation is ongoing.
This ANDA is recommended for tentative approval.

9. Gary Buehler Date 11/30/04
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 2 Peter Chen Date 11/30/04
Review Support Branch Initials PC
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
1226 Time notified of approval by phone 1236 Time approval letter faxed
FDA Notification:
11/30/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/30/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

## OGD APPROVAL ROUTING SUMMARY

ANDA # 76-703 Applicant Apotex Inc.
Drug Desmopressin Acetate Nasal Spray Strength(s) 0.01%

**APPROVAL** ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

**REVIEWER:** **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 6/W 2005 Date 1/27/05
Initials MMS Initials AW for

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 17-922
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked 1/27/05
If Para. IV Certification- did applicant Nothing Submitted X
Notify patent holder/NDA holder Yes ☑ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐ Study Submitted ☐
Has case been settled: Yes ☑ No ☐ Date settled: 12/27/2004
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: 180 Day exclusivity for this Drug Product is given the w/Date of NDA ——— which
Comments: was 1st applicant to submit P IV certs to all patents covering this product.
Barr has entered into settlement agreement & dismissals/Pending for '931 patent. Apotex/Ferring must also wait 30 month stay as settlement agreement does not address invalidity or non-infringement of the '931 patent

2. Project Manager Peter Chen Team 2
Review Support Branch
Date 1/3/05 Date 1/3/05
Initials PC Initials PC

Original Rec'd date 3/26/03 EER Status Pending ☐ Acceptable ☑ OAI ☐
Date Acceptable for Filing 4/1/03 Date of EER Status 2/4/04
Patent Certification (type) IV Date of Office Bio Review 11/6/04
Date Patent/Exclus.expires _____ Date of Labeling Approv. Sum 9/21/04
Citizens' Petition/Legal Case Yes ☐ No ☐ Labeling Acceptable Email Rec'd Yes ☐ No ☐
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes ☐ No ☐
First Generic Yes ☐ No ☑ Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☑ No ☐ Modified-release dosage form: Yes ☐ No ☑
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☑ Date 11/30/04
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ NA Date 1/25/04
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: see revisions

4. Div. Dir./~~Deputy~~ Dir.
Chemistry Div. I ~~I OR II~~I
Date 1/26/05
Initials RRC
Comments:

The Gmc section remains satisfactory since TA'd

**REVIEWER:** **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. This ANDA was tentatively approved on 11/30/04. In addition, a related ANDA 74-830/Bausch+Lomb was approved 1/25/99 (refrigerated product).

6. Vacant RLD=DDAVP Nasal Spray, 0.01 mg/spray (non-refrigerated)
Deputy Dir., DLPS Date_____
Aventis Pharmaceutical Products, Inc. NDA 17-922 (003) Initials_____

7. Peter Rickman Date 1/27/05
Director, DLPS Initials Request for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 3/4/04 Verified 1/26/05. No O.A.I. alerts noted. Refer to the administrative sign-off form completed at the time of the tentative approval issued on 11/30/04. On 12/9/04, Apotex (Novex) submitted a minor amendment to request final approval on the basis of a license agreement between Ferring B.V., Aventis and Apotex. The ongoing patent litigation was also dismissed. FPL as previously submitted remains satisfactory for approval (per Gail 1/24/05 Grace Chen). CMC remains satisfactory for approval 1/26/05. Methods validation has been completed.

8. Robert L. West Date 1/27/2005
Deputy Director, OGD Initials Concur
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Novex made paragraph IV Certifications to the '931, '143, '850, and '402 patents. Novex was sued within the 45-day period only on the '931 patent.
Based upon the signed license agreement and dismissal of the patent litigation, this ANDA is recommended for approval. Ferring+Aventis have waived the 30-month stay.

9. Gary Buehler Date 1/27/05
Director, OGD Initials GB
Comments: for non-refrigerated product
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 2 Peter Chen Date 1/27
Review Support Branch Initials
NH Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
9:47 AM Time notified of approval by phone 9:56 AM Time approval letter faxed
FDA Notification:
1/27 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/27 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-703

# CORRESPONDENCE

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9989 • FAX: (847) 573-1001

OK 5/29/03
Concur. 29-MAY-2003
505(j)(2)(A)(i)

March 26, 2003

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Desmopressin Acetate Nasal Solution
0.01% (Nasal Spray)
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc. of Ontario, Canada, is hereby forwarding an original abbreviated new drug application (ANDA) for Desmopressin Acetate Nasal Solution, 0.01%.

Enclosed is an archival copy under blue cover, a chemistry review under red cover, and the bioavailability/bioequivalence review section under orange cover and a field copy under a burgundy cover.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

ANDA 76-703

MAY 30 2003

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

Dear Madam:

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

Reference is made to the telephone conversation dated May 23, 2003 and your correspondence dated May 29, 2003.

NAME OF DRUG: Desmopressin Acetate Nasal Spray, 0.01 mg/spray

DATE OF APPLICATION: March 26, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 1, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

**CONTENTS OF THE NOTICE**

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

**SENDING THE NOTICE**

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

    1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

**DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE**

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

**DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME**

You are requested to submit an amendment to this application that is plainly marked on the cover sheet A PATENT AMENDMENT with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is

applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

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

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

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-703
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB 30-MAY-2003 date
HFD-615/CBina, CSO date
Word File
V:\FIRMSNZ\NOVEX\LTRS&REV\76703.ACK
F/T

**ANDA Acknowledgment Letter!**

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

July 3, 2003

NEW CORRESP
NC

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

**PATENT AMENDMENT**

RE: Desmopressin Acetate Nasal Solution
0.01% (nasal spray)
ANDA No. 76-703
Patent Numbers: 5482931, 5500413, 5674850 and 5763407

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, is hereby forwarding in duplicate the patent amendment for the above referenced patent numbers.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
1-847-279-7740

RECEIVED
JUL 0 8 2003
OGD/CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

ORIG AMENDMENT

August 19, 2003

N/AF

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

**LABELING AMENDMENT**

RE: Desmopressin Acetate Nasal Solution
0.01% (nasal spray)
ANDA No. 76-703

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma in Canada, is hereby forwarding in duplicate a labeling amendment in response to the FDA label deficiency letter dated July 14, 2003.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
847-279-7740

RECEIVED
AUG 21 2003
OGD/CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

NAI
9/9/03

August 25, 2003

NEW CORRESP
NC

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

**PATENT AMENDMENT**

RE: Desmopressin Acetate Nasal Solution
0.01% (nasal spray)
ANDA No. 76-703

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, is hereby forwarding in duplicate the patent amendment for the above referenced product. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
1-847-279-7740

RECEIVED
AUG 2 7 2003
OGD/CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

December 23, 2003

Mr. Peter Chen
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA,
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

Dear Mr. Chen:

**Re: MINOR AMENDMENT:**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray),**
**ANDA No. 76-703**

Further to your Minor Amendment letter received at Apotex Corp on September 23, 2003, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2, and a signed Field Copy Certification can be found in Attachment No. 3.

*A. Deficiencies:*

*1. We have following comments regarding the drug substance:*

*a.* [ ]

**Response:**

[ ]

RECEIVED
DEC 2 4 2003
OGD/CDER

.../cont'd

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

12/23/2003 SPONSOR LETTER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

- R/ from Aventis
- No R/ from Ferring B.V.
- Ferring was contacted today (Paul Bonnici) and asked to provide fax. of receipt.
S. Middleton 6/2/04

May 11, 2004

Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

**Re: PATENT AMENDMENT**
**Desmospressin Acetate Nasal Solution, 0.01% (Nasal Spray); ANDA No. 76-703**

Further to our Abbreviated New Drug Application (ANDA No. 76-703) dated March 25, 2003, and in accordance with 21 CFR 314.95(e), please find enclosed the return receipts from Aventis and Ferring AB, as an evidence of patent notification to the patent holders. A signed Application Form FDA 356h has been enclosed.

Please note that the return receipt from Ferring BV is unavailable, however, our lawyer advised us that Ferring BV received our Notice Letter on July 14, 2003.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc, MBA
Director, Regulatory Affairs

PB:sf

Encl.

RECEIVED
MAY 1 3 2004
OGD/CDER

3.1

NOVEX PHARMA ORIGINAL

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

May 20, 2004

ORIG AMENDMENT
N/AM

Mr. Peter Chen
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen:

**Re: MINOR AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray),**
**ANDA No. 76-703**

Further to your Minor Amendment letter dated February 17, 2004, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2, and a signed Field Copy Certification can be found in Attachment No. 3.

*A. Deficiencies:*

*1.* [redacted]

**Response:**

[redacted] Copies of these specifications can be found in Attachment Nos. 4 and 5.

RECEIVED
MAY 2 1 2004
OGD/CDER

.../cont'd

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

5/20/2004 SPONSOR LETTER

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

APPEARS THIS WAY
ON ORIGINAL

MODE = MEMORY TRANSMISSION START=JUN-07 10:02 END=JUN-07 10:03

FILE NO.=406

| STN NO. | COMM. | ABBR NO. | STATION NAME/TEL NO. | PAGES | DURATION |
|---|---|---|---|---|---|
| 001 | OK | a | 918473532982 | 002/002 | 00:00:24 |

-CDER OGD DOC RM -

********** - - ***** - - **********

# BIOEQUIVALENCY AMENDMENT

ANDA 76-703

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 0 4 2004

APPLICANT: Apotex Corp. U.S. Agent for Novex Pharma

TEL: 847-279-7740

FAX: 847-353-2982

ATTN: Marcy Macdonald

PROJECT MANAGER: 301-827-5847

FROM: Aaron Sigler

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 26, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Desmopressin Acetate Nasal Spray, 0.01 mg/spray.

Reference is also made to your amendment(s) dated: .

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

**SPECIAL INSTRUCTIONS:**

JUN 04 2004

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-703 APPLICANT: Novex Pharma

DRUG PRODUCT: Desmopressin Acetate Nasal Spray 0.01mg/spray

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

You did not provide an expiration date for the test lot. Please provide an expiration date for the test lot# 2X130.

The three Spray Pattern distances from the actuator orifice submitted were not at least 3cm apart. Please perform spray pattern testing at 2 distances from the actuator orifice, within the range of 3cm to 7cm, that are at least 3cm apart. You can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for bioequivalence evaluation. Alternatively, you can use automated analysis of the pattern area and ovality ratios of the test and reference products at the beginning of life stage for bioequivalence evaluation.

Sincerely yours,

Barbara McDaniel

Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

6/15/04 MF
XP C Ajit 203-3860
4/24/04

June 07, 2004

Ms. Saundra Middleton
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Middleton:

**Re: PATENT AMENDMENT – REQUEST FOR ADDITIONAL INFORMATION**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray); ANDA No. 76-703**

Further to our telephone conversation on June 02, 2004 regarding the patent notification to patent holders for the above product, please find enclosed the Plaintiff's Objections and Responses letter from Ferring's counselor as additional evidence to confirm the delivery date of the Notification Letter to Ferring BV. This information can be found in Specific Responses and Objections, Interrogatory No. 4. A signed Application Form FDA 356h has been enclosed.

Should you require any further information, or have any questions or comments regarding the enclosed. Please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

RECEIVED
JUN 0 8 2004
OGD/CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

ORIGINAL

XA

June 10, 2004

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Mr. Buehler:

**Re: Desmopressin Acetate Nasal Solution (Nasal Spray), 0.01%, ANDA No. 76-703**

There has been some restructuring within the Apotex Group of Companies to formally reflect that they are part of Apotex Inc. Effective immediately, the names of the various sites that make up the Apotex Group have changed.

Novex Pharma (a Division of Apotex Inc.) will now be named Apotex Inc. and will be distinguished from other locations by referring to it as the Richmond Hill Site.

A signed Application Form FDA 356h has been provided with this letter for the above-mentioned product. A complete listing of Novex Pharma's approved ANDAs and ANDAs currently under review by the Agency has been appended to this letter.

If you have any questions, please do not hesitate to contact me by phone at (905) 508-2396, by Fax at (905) 884-0357 or email at pbonnici@apotex.com.

Sincerely,
APOTEX INC. – Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

RECEIVED
JUN 14 2004
OGD / GDEP

4.1

ORIGINAL

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimilie 905 884-9876

July 08, 2004

Mr. Aaron Sigler
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Dear Mr. Sigler:

**Re: BIOEQUIVALENCY AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01 % (Nasal Spray),**
**ANDA No. 76-703**

Further to your Bioequivalency Amendment letter dated June 04, 2004, we are pleased to provide you with our response in triplicate (Archival, Pharmacokinetic and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

*You did not provide an expiration date for the test lot. Please provide an expiration date for the test lot # 2X130.*

**Response:** Please note that no expiry date has been set for Lot No. 2X130 as this is a submission batch. The batch was manufactured on May 15, 2002.

*The three Spray Pattern distances from the actuator orifice submitted were not at least 3 cm apart. Please perform spray pattern testing at 2 distances from the actuator orifice, within the range of 3 cm to 7 cm, that are at least 3 cm apart. You can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for bioequivalence evaluation. Alternatively, you can use automated analysis of the pattern area and ovality ratios of the test and reference products at the beginning of life stage for bioequivlaence evaluation.*

RECEIVED
JUL 0 9 2004
OGD / CDER

.../cont'd

**Response:**

[redacted]

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

APPEARS THIS WAY
ON ORIGINAL

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

July 27, 2004

Office of Generic Drugs, HFD-600
CDER, FDA,
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AA

Dear Sir/Madam:

**Re: GRATUITOUS AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), ANDA No. 76-703**

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray). This Gratuitous Amendment has been provided in triplicate (Archival, Review and Field copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment No. 1, and a Field Copy Certification can be found as Attachment No. 2.

We would like to inform the Agency of a change to the _____ range, an In-Process check parameter during the filling/packaging process for Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray). The _____ range is being changed from _____ _____. The supporting data for this change is provided as Attachment No. 3.

The data was developed as a result of the product improvement process for our domestically approved product, Apo-Butorphanol (Butorphanol Tartrate Nasal Spray), 10mg/ mL. The primary packaging components (i.e. bottle and cap) for Apo-Butorphanol are identical to those for Desmopressin Acetate Nasal Solution. Thus, the _____ range is applicable to our Desmopressin Acetate Nasal Solution as well.

..../cont'd

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

ORIGINAL

5.1

July 29, 2004

MC/BIO

Mr. Aaron Sigler
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

**Re: REQUEST TO WITHDRAW BIOEQUIVALENCY AMENDMENT for Desmopressin Acetate Nasal Solution, 0.01 % (Nasal Spray),ANDA No. 76-703**

Further to our application for Desmopressin Acetate Nasal Solution, 0.01 % (Nasal Spray), we would like to withdraw our Bioequivalency Amendment submitted on July 08, 2004. Please note that we are in the process of preparing a response to the bioequivalency deficiency dated June 04, 2004. An Application Form FDA 356h has been prepared and is enclosed.

Should you have any questions or comments regarding the above, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. - Richmond Hill Site

P.B

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

RECEIVED
JUL 30 2004
OGD/CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 04, 2004

ORIG AMENDMENT

N/A B

Mr. Aaron Sigler
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

**Re: BIOEQUIVALENCY AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01 % (Nasal Spray), ANDA No. 76-703**

Further to your Bioequivalency Amendment letter dated June 04, 2004, we are pleased to re-submit our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1, and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

Please note that on July 29, 2004, a request was submitted to withdraw our bioequivalency amendment dated July 08, 2004. Thus, at this time, the amendment provided is appropriate for review.

*You did not provide an expiration date for the test lot. Please provide an expiration date for the test lot # 2X130.*

**Response:** Please note that no expiry date has been set for Lot No. 2X130 as this is a submission batch. The batch was manufactured on May 15, 2002.

*The three Spray Pattern distances from the actuator orifice submitted were not at least 3 cm apart. Please perform spray pattern testing at 2 distances from the actuator orifice, within the range of 3 cm to 7 cm, that are at least 3 cm apart. You can manually analyze the Dmax and Ovality ratio of the test and reference products at the beginning of life stage for bioequivalence evaluation. Alternatively, you can use automated analysis of the pattern area and ovality ratios of the test and reference products at the beginning of life stage for bioequivlaence evaluation.*

RECEIVED .../cont'd
AUG 0 5 2004
OGD / CDER

**Response:** As per the Agency's suggestion, we have repeated the spray pattern analysis using a manual (TLC) technique, Test Method – PD163, (Issue No. 1), Spray Pattern Determination for Desmopressin Acetate Nasal Spray. A copy of the test method has been provided in Attachment No. 3.

In accordance with the April 2003 draft guidance, BA/BE Studies for Nasal Aerosols and Nasal Sprays For Local Action, Dmax and the Ovality ratio should be used for the statistical evaluation of BE for manual analyses. The T/R ratios for Dmax and Ovality are within the 0.9 - 1.11 range at distances of 3 cm and 6 cm from the actuator orifice and therefore, the test and reference products are equivalent in spray pattern. Images of the 20% representative spray pattern have been included in Attachment No. 4 for review. An electronic copy of the spray pattern data in SAS format has also been enclosed in this amendment.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 24, 2004

ORIG AMENDMENT
NDA

Peter Chen
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen:

**Re: MINOR AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), ANDA No. 76-703**

Further to your Minor Amendment letter dated July 28, 2004, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2, and a signed Field Copy Certification can be found in Attachment No. 3.

*A. Deficiencies:*

*1.* [redacted]

RECEIVED
AUG 25
OGD

RECEIVED
AUG 25 2004
OGD / CDER

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

8/24/2004 SPONSOR LETTER

2. *Bioequivalence has not been established. Please reply to the bioequivalence deficiency letter sent to you by facsimile on June 4,2004,*

   **Response:** The bioequivalence deficiency letter sent to us by facsimile on June 4, 2004 was responded to the Agency on August 04, 2004.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. – Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 27, 2004

ORIG AMENDMENT

RECEIVED
AUG 3 0 2004
OGD/CDER

Office of Generic Drugs, HFD-600
CDER, FDA,
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NME

Dear Sir/Madam:

**Re: GRATUITOUS LABELING AMENDMENT**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), ANDA No. 76-703**

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Labeling Amendment to our unapproved application for Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray). This Gratuitous Labeling Amendment has been provided in duplicate (Archival and Review copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment No. 1.

This Gratuitous Labeling Amendment is submitted as a result of the change in our standard labeling format and to update the labeling following a revision to the Reference Listed Drug labeling, DDAVP® Nasal Spray, manufactured by Aventis Pharmaceuticals Inc. A copy of the DDAVP® labeling has been provided in Attachment No. 2 for reference.

In accordance with 21 CFR 314.94 (a)(8)(iv), a side-by-side comparison of Apotex's final printed container (bottle) label, carton and package insert (prescribing information and patient instruction guide) provided in this Amendment and those provided in our Labeling Amendment submitted on August 18, 2003, with all differences annotated and explained have been provided in Attachment No. 3.

An electronic copy of the labeling has been provided with the Review copy only. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the enclosed labeling for the bottle, cartons, and package insert are a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, Apotex Inc. will notify the agency, as necessary.

..../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or FAX your requests to (905) 884-0357.

Yours sincerely,
APOTEX INC. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

APPEARS THIS WAY
ON ORIGINAL

9.1

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

December 29, 2004

Mr. Gary Buehler
Director, Office of Generic Drugs - HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Dear Mr. Buehler:

**Re: MINOR AMENDMENT – FINAL APPROVAL REQUESTED**
**Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), ANDA No. 76-703**

Further to your tentative approval letter dated November 30, 2004, we are pleased to provide you with our Minor Amendment – Final Approval Requested letter in duplicate (Archival and Review). For ease of review, we have enclosed a copy of your tentative approval letter as Attachment No. 1 of this amendment. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

In supporting of this request, please find enclosed a signed Settlement Agreement (Attachment No. 3) and a signed License Agreement (Attachment No. 4) between Ferring B.V., Aventis Pharmaceuticals Inc., and Apotex Inc. A signed Stipulation of Dismissal has also been included in Attachment No. 5.

Please note that a Gratuitous Labeling Amendment was submitted on August 27, 2004 as a result of a change to our standard labeling format and to update the labeling following a revision to the Reference Listed Drug labeling. Please note however, that no changes have been made to the chemistry, manufacturing and control data, or to any other data under which tentative approval was granted on November 30, 2004.

RECEIVED
DEC 30 2004
OGD / CDER

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,

for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl

APPEARS THIS WAY
ON ORIGINAL