

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-333**

**MEDICAL REVIEW**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center For Drug Evaluation and Research

DATE: August 29, 2001  
FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
TO: NDA 21-333  
Desmopressin acetate nasal spray  
Ferring Pharmaceuticals, Inc.  
SUBJECT: NDA review issues and recommended action

**Background**

Desmopressin acetate (DDAVP) is approved for diabetes insipidus of central (pituitary or hypothalamic) origin as well as for nocturnal enuresis in children. The subject of this application is a refrigerated formulation of desmopressin acetate that is bioequivalent to the room-temperature-stored formulation also manufactured by Ferring and marketed by Aventis under NDA 17-922. The current application is cross-referenced to that NDA and is a 505(b)(1) application insofar as Ferring has been given right-of-reference to that application.

**Supportive information**

There are no new data submitted with this application. It fully cross-references clinical, CMC, preclinical, biopharmaceutics information in NDA 17-922. The labeling is in order with minor changes relative to the approved package insert.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

The product is to be called "Desmopressin acetate nasal spray."

**Establishment inspections**

The inspection of the Ferring AB manufacturing facility in Malmo, Sweden revealed several deficiencies and lead to a "Withhold" recommendation from the Office of Compliance, CDER. In brief, the issues raised related to the absence of data on the compatibility of the \_\_\_\_\_ used in the filling operations with the drug formulation. Specifically, there is an interaction with the chlorobutanol added \_\_\_\_\_ to this substance \_\_\_\_\_ . These deficiencies must be addressed and a satisfactory inspection conducted prior to approval.

A Form 483 was issued to the sponsor of May 23, 2001.

NDA # 21-333, Ferring  
Drug: Desmopressin acetate nasal spray  
Proposal: refrigerated formulation  
08/29/01

**Recommendation**

This application is approvable pending a satisfactory establishment inspection after the sponsor has addressed the deficiencies listed on the 483 form.

NDA # 21-333, Ferring  
Drug: Desmopressin acetate nasal spray  
Proposal: refrigerated formulation  
08/29/01

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David Orloff  
8/29/01 06:53:20 PM  
MEDICAL OFFICER

**MEDICAL TEAM LEADER'S REVIEW OF NEW DRUG APPLICATION**

**NDA #: 21-333**

**Product name: desmopressin acetate nasal spray**

**Sponsor: Ferring Pharmaceuticals, Inc.**

**Date of Submission: November 3, 2000**

**Date Review Completed: July 18, 2001**

**Background**

Desmopressin acetate is a synthetic form of arginine vasopressin, a neurohormone involved in the regulation of water metabolism. The marketed product is a formulation stored at room temperature which is manufactured by Ferring Pharmaceuticals and marketed by Aventis Pharmaceuticals, the holder of the new drug application (NDA #17-922). Desmopressin acetate is indicated for the treatment of primary nocturnal enuresis and central diabetes insipidus.

Ferring Pharmaceuticals also manufactures a refrigerated formulation of desmopressin acetate that is bioequivalent to the room temperature formulation. Ferring Pharmaceuticals has submitted an application for the refrigerated formulation for the same indications as the product marketed by Aventis Pharmaceuticals. This is a 505(b)(1) application with complete cross-referencing to the approved NDA 17-922 for clinical, toxicology, and CMC data.

**Proposed Labeling**

A comprehensive labeling review was undertaken by consumer safety officer. The specific changes to the approved package insert included:

- replacing the brand name DDAVP Nasal Spray (desmopressin acetate 0.01% nasal solution with desmopressin acetate nasal spray
- changing the NDC number and name of manufacturer

The following changes were also made to the Patient Instruction Guide:

- replacing the brand name DDAVP Nasal Spray (desmopressin acetate 0.01% nasal solution with desmopressin acetate nasal spray
- changing the number and amount (in mcg) of drug delivered from 25 doses of 10 mcg each to 50 doses of 10 mcg each
- instructions for storage under refrigerated conditions of 2 to 8° C (36 to 46°F)

**Review Issues**

There are no new clinical data submitted for review of this application. A consult was submitted to the Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580) to determine if the labeling for primary nocturnal enuresis was acceptable. The labeling was acceptable with DRUDP with the exception for the following sentence under the INDICATIONS and USAGE section:

Recommendations were made by DRUDP to remove the phrase, "~~\_\_\_\_\_~~" as this was considered a broad-based claim for which there were no supportive data.

Other review disciplines included:

- Clinical Pharmacology reviewer recommended a Pharmacokinetics subsection to be included under the CLINICAL PHARMACOLOGY section of the label.
- OPDRA specific recommendations to the container and carton labels.

#### **Other Administrative Issues**

##### **Financial Disclosure Information**

No financial disclosure information required since no clinical studies were conducted under this NDA.

##### **Pediatric Study Requirements**

There are two indications recommended for this drug product.

1. Treatment of primary nocturnal enuresis is recommended in children ages 6 years and older and short term studies (4-6 weeks) have been conducted in this population.
2. Treatment of central or cranial diabetes insipidus (DI) is recommended in children ages 3 months and older.

Pediatric study requirements for primary nocturnal enuresis in children under age 6 should be waived since primary nocturnal enuresis is difficult to diagnose in children below age 6. Nighttime urinary incontinence below this age is not uncommon and is rarely considered pathologic to warrant treatment with desmopressin acetate.

Central DI can be due to several factors including congenital abnormalities, structural defects, infections, and head trauma (including neurosurgery). The number of patients younger than 3 months presenting with central DI is small making it difficult to conduct adequate and well-controlled studies in this population. The pediatric study requirements in central DI patients younger than 3 months should be deferred. The sponsor should evaluate whether data from published literature are available and sufficient for labeling in this population.

##### **Specific Recommendations to be Conveyed to Sponsor**

Under the INDICATIONS AND USAGE section of the label, the following recommendation is made to the 3<sup>rd</sup> paragraph:

*The use of desmopressin acetate nasal spray 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.*

**Recommendations on Application**

Pending the recommended changes to the proposed label as per DRUDP, Clinical Pharmacology, and OPDRA, this NDA should be approved.

Mary H. Parks, MD  
Medical Team Leader  
Division of Metabolic and Endocrine Drug Products  
HFD-510

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/s/  
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Mary Parks  
7/16/01 03:41:30 PM  
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David Orloff  
7/17/01 06:43:43 PM  
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Concur with Dr. Parks' recommendation. There will be no separate Division Director memo regarding this application.

NDA 21-333

**Medical Officer's Memorandum: Review of Label**

**Submitted:** October 27, 2000

**Received:** November 3, 2000

**Consult requested:** January 23, 2001

**Consult assigned:** February 12, 2001

**MOR complete:** March 22, 2001

**Sponsor:** Ferring Pharmaceuticals, Inc.

**Drug product:** Minirin™ Nasal Spray

**Indication:** 1. Diabetes Insipidus  
2. Primary Nocturnal Enuresis

**Brief summary:**

On October 27, 2000, Ferring Pharmaceuticals submitted this new drug application (NDA # 21-333) to the Division of Metabolic and Endocrine Drug Products (DMEDP) for a refrigerated formulation of desmopressin (DDAVP) nasal spray. The drug product will be indicated for the treatment of diabetes insipidus and primary nocturnal enuresis.

Currently, Ferring manufactures the **identical** refrigerated product under NDA 17-922. Aventis Pharmaceuticals (not Ferring) is the owner of NDA # 17-922. In the NDA cover letter, Ferring informs the Agency that Aventis does not market the refrigerated formulation. Instead, Aventis markets a room temperature DDAVP nasal spray for "commercial reasons". The room temperature product is purported to be a bioequivalent re-formulation of the original refrigerated product.

DMEDP is the primary reviewing Division for this 505(b)(1) application. This application cross-references NDA #17-922 for all clinical, toxicology, and CMC information except for the proposed labeling and environmental assessment. DRUDP was asked to perform a review of the labeling with particular emphasis on the nocturnal enuresis indication.

**Materials reviewed:**

The sponsor provided the approved package inserts for the currently marketed product (under NDA # 17-922) as well as the new refrigerated product (NDA #21-333).

The following revisions were noted:

- The name of drug product was changed from Desmopressin Acetate Nasal Spray to Minirin™ nasal spray
- The product will be manufactured for Ferring Pharmaceutical Inc. \_\_\_\_\_

The remainder of the approved label was reviewed in detail.

**Reviewer's comment:**

Review of the approved labeling was performed to assess for gross inaccuracies or urologic misinformation. This medical officer did not perform a review of the original clinical trial data that supported the nocturnal enuresis indication for NDA 17-922.

1. There did not appear to be any inaccurate or misleading information in the approved labeling.

2. The following sentence in the third paragraph of the "Indications and Usage" section was notable:

The broad-based claim, \_\_\_\_\_, would require substantial controlled clinical trial data. Unless such data is available, it would seem reasonable to request removal or revision of this \_\_\_\_\_ claim.

**Recommended regulatory action:** This consult should be forwarded to DMEDP and submitted to the archival file for NDA #21-333

A Batra, MD  
Medical Officer  
Division of Reproductive and Urologic Drug Products  
Arch NDA 21-333  
HFD-580/Div File  
HFD-580/SAllen/DSHames/MHirsch/KColangelo

/s/

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