

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022517Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 15, 2018

From: Mark R. Seggel, Ph.D.
Application Technical Lead
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: OPQ IQA for NDA 22517
Nocurna (desmopressin acetate) Sublingual Tablets

Subject: Final Recommendation - APPROVAL

Summary:

The OPQ Integrated Quality Assessment (IQA) dated June 11, 2018, concluded that this 505(b)(1) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (package insert, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201.

The NDA was otherwise complete and adequate from the OPQ perspective.

The major labeling deficiencies identified in the June 11, 2018 IQA were related to the established name, expression of strength, and dosage form. The issue was previously discussed with Ferring in a June 8, 2018 teleconference. Revisions to the package insert, medication guide, and container/carton labels, were also communicated to Ferring in correspondence dated May 25, 2018, June 8, 2018, June 14, 2018 and June 15, 2018. See Labeling Review Notes below.

On June 15, 2018, Ferring acknowledged the requested changes and provided written agreement to revise the labeling accordingly (email to Nenita Crisostomo, DBRUP, see the **Attachment**). This agreement is deemed sufficient to allow OPQ to make a final recommendation for this application. Revised, final labeling will be formally submitted to the NDA.

Recommendation:

This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

{see digital signature page}

Labeling Review Notes:

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment (0055)	06/05/18	Labeling
Amendment (0056)	06/14/18	Labeling

The major labeling deficiencies identified in the June 11, 2018 IQA related to the established name, expression of strength, and dosage form.

Ferring proposed:

Nocdurna (desmopressin) orally disintegrating sublingual tablets,
with strengths expressed based on desmopressin (25 mcg and 50 mcg desmopressin).

In consultation with the OPQ/OPPQ Product Quality Labeling (PQL) team, it was determined that the appropriate product title is:

Nocdurna (desmopressin acetate) sublingual tablets,
with strengths expressed based on desmopressin acetate (27.7 mcg and 55.3 mcg of desmopressin acetate, equivalent to 25 mcg and 50 mcg of desmopressin, respectively).

This determination is based, in part, on the need for consistency across the approved desmopressin acetate products. Because the product is administered by placing under the tongue, the correct dosage form is 'sublingual tablets.'

On June 8, 2018, a teleconference between FDA and Ferring was held to discuss this issue. Ferring presented their arguments for keeping their proposed format which were primarily based on their perceived safety concerns. These arguments appear more to do with brand distinction for marketing purposes than actual safety. FDA explained why the proposed format and strength were not acceptable based on CDER policy. Revised carton and blister labeling incorporating the changes requested by the FDA was submitted by Ferring on June 14, 2018.

See FDA correspondence dated May 25, 2018, June 8, 2018, June 14, 2018 and June 15, 2018, in which revisions to the package insert, medication guide, and container/carton labels, were communicated to Ferring. Of note, Ferring was asked to revise the list of inactive ingredients in Section 11 of the package insert and on the cartons from "fish gelatin" to "gelatin, NF (fish source)." Including the source of gelatin in this format satisfies inactive ingredient nomenclature requirements while bringing attention to the origin, fish, to which patients with fish allergies may be sensitive.

Revisions to the storage statements to include a range of temperatures, i.e., 20°C to 25°C, and other standard language were also proposed.

On June 15, 2018, Ferring acknowledged the requested changes and provided written agreement to revise the labeling accordingly (email to Nenita Crisostomo, DBRUP see the **Attachment**). This agreement is deemed sufficient to allow OPQ to make a final recommendation of Approval for this application. Revised, final labeling will be formally submitted to the NDA.

Additional Comments: FDA has advised Ferring that the tablet embossing, 25 and 50, remains acceptable.

Attachment:

Hello CMC Team,

Ferring agrees to all items that we sent to them this morning. They mentioned this morning about Section 3, as follows. They just want to let you know that the embossment on the tablet remains 25 and 50.

1 DOSAGE FORMS AND STRENGTHS

Sublingual tablets:

- 27.7 mcg of desmopressin acetate (equivalent to 25 mcg of desmopressin): White, round, with 25 on one side.
- 55.3 mcg of desmopressin acetate (equivalent to 50 mcg of desmopressin): White, round with 50 on one side.

Please let me know what you think.

Thanks,
nita

From: Abhijit.Pangu@ferring.com [mailto:Abhijit.Pangu@ferring.com]
Sent: Friday, June 15, 2018 12:33 PM
To: Crisostomo, Nenita <Nenita.Crisostomo@fda.hhs.gov>
Cc: US1RegulatoryAffairs.US1RegulatoryAffairs@ferring.com;
Brenda.Marczi@ferring.com
Subject: RE: NDA 22517 NOCDURNA: CMC

Dear Nita:

We acknowledge and hereby agree to the changes suggested by the FDA CMC

review team to the USPI and carton labels and plan to submit the updated labels for review in the subsequent eCTD sequences.

As discussed, please provide us clarification on the debossing on the tablets – "25" and "50" that is included in USPI Section 3, version dated June 14, 2018.

Thank you,
AJ

Abhijit (AJ) Pangu
Director, US Regulatory Affairs
Ferring Pharmaceuticals Inc.
100 Interpace Parkway, Parsippany, NJ 07054
+1 (973) 206 4864 | abhijit.pangu@ferring.com



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Mark
Seggel

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Date: 6/15/2018 06:31:09PM

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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

**NDA 22517
Review # 5**

NOCDURNA (desmopressin acetate) Sublingual Tablets

Drug Name/Dosage Form	desmopressin acetate sublingual tablets
Strength	27.7 mcg and 55.3 mcg of desmopressin acetate, equivalent to 25 mcg and 50 mcg of desmopressin, respectively.
Route of Administration	Sublingual
Rx/OTC Dispensed	Rx
Applicant	Ferring Pharmaceuticals Inc.
US agent, if applicable	not applicable

SUBMISSION(S) REVIEWED*	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission Following Complete Response (0039)	12/21/2017	Drug Substance, Drug Product/Labeling, Facilities
Amendment (0042)	02/07/2018	Drug Substance
Amendment (0044)	03/09/2018	Labeling
Amendment (0048)	05/09/2018	Labeling

* See Application and Review History for list of previous reviews and reviewers.

Quality Review Team*

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	BII / DNDAPI / ONDP
Drug Product	Hong Cai	BV / DNDPII / ONDP
Labeling	Hong Cai	BV / DNDPII / ONDP
Facilities	Allison Aldridge	BIII / DIA / OPF
RBPM	Thao Vu; Florence Bamidele	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP

* See Application and Review History for list of previous reviews and reviewers.

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
8396	II	PolyPeptide Laboratories (Sweden)	Synthesis of desmopressin acetate	Adequate	February 15, 2018 J. Leginus	
(b) (4)	III		(b) (4)	N/A		

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 65890	Ferring FE992026 (desmopressin melt)
New Drug Application	NDA 19955*	DDAVP Tablets
New Drug Application	NDA 17922*	DDAVP Intranasal

* Original owned by Sanofi-Aventis; subsequently acquired by Ferring.

C. Application and Product Quality Review History

Document	Date	Document Type	Comments
Resubmission	12/21/2017		
CRL	01/30/2015		<i>Labeling not finalized</i>
Ysem, Xavier J	01/27/2015	Memo archived in Panorama*	<i>Memo – Approval Recommendation pending Facilities</i>
Class 2 Resubmission in response to 01/30/13 CRL	07/31/2014		
Dispute Appeal Denied	01/15/2014		
Request for Dispute Resolution	11/21/2013		
Mahayni, Houda	09/09/2013	REV-QUALITY-21 (Primary Review)	Bph Review 090913
Resubmission / Incomplete	07/17/2013		
CRL	01/30/2013		<i>Labeling not finalized</i>
Mahayni, Houda	01/08/2013	REV-QUALITY-21 (Primary Review)	Bph Review 010813

Ysem, Xavier J	01/07/2013	REV-QUALITY-21 (Primary Review)	ChemRev#4
Metcalfe, John W	01/03/2013	REV-QUALITYMICRO-21 (Primary Review)	MicroReview#2
Ysem, Xavier J	12/07/2012	REV-QUALITY-03 (General Review)	ChemRev#3
Mahayni, Houda	08/30/2012	REV-QUALITY-06 (Filing Review)	Bph Filing Review
Class 2 Resubmission	07/30/2012		
CRL	04/22/2010		<i>Labeling not finalized</i>
Hill, John C	04/19/2010	REV-QUALITY-03 (General Review)	Memo – Establishment Evaluation NDA Approval Recommendation
Peri, Prasad	03/23/2010	REV-QUALITY-03 (General Review)	Secondary Review
Hill, John C	03/09/2010	REV-QUALITY-03 (General Review)	ChemRev#2
Metcalfe, John W	02/12/2010	REV-QUALITYMICRO-01 (General Review)	MicroReview#1
Hill, John C	12/02/2009	REV-QUALITY-04 (Review Noted (NAI))	NAI/ no cmc
Hill, John C	10/21/2009	REV-QUALITY-03 (General Review)	ChemRev#1
Tran, Suong T	08/11/2009	REV-QUALITY-03 (General Review)	Initial Quality Assessment 25 mcg and 100 mcg desmopressin orally disintegrating tablets
Original Submission	06/22/2009		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Ferring Pharmaceuticals' 505(b)(1) New Drug Application #22517, for Nocdurna (desmopressin acetate) sublingual tablets, is not ready for approval.

Labeling negotiations have not been completed and there is no agreement on the content and format of the final product labeling. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201 (see the **List of Deficiencies** at the end of this review).

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

Ferring's claim of a categorical exclusion for the preparation and submission of an Environmental Assessment is acceptable.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	NOCDURNA is indicated for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.
Duration of Treatment	Indefinite
Maximum Daily Dose	Women: 25 mcg desmopressin Men: 50 mcg desmopressin
Alternative Methods of Administration	Not Applicable

NOCDURNA (desmopressin acetate) Sublingual Tablets is a sublingual tablet formulation containing 27.7 mcg and 55.3 mcg of desmopressin acetate, equivalent to 25 mcg and 50 mcg of desmopressin, respectively. Desmopressin is a vasopressin analog with antidiuretic activity. The product is designed to disintegrate and release drug when placed under the tongue. NOCDURNA is administered sublingually one hour before bedtime without water.

The daily dose for women is 27.7 mcg and for men is 55.3 mcg.

The inactive ingredients are fish gelatin, mannitol, and anhydrous citric acid. All meet USP/NF monograph requirements. Each sublingual tablet weighs about 23 mg and contains approximately (b) (4) % or (b) (4) % desmopressin by weight.

The product is formed by (b) (4)

The drug product specification includes tests for appearance, identification, assay, degradation products, uniformity of dosage units (by weight variation), microbiological quality, (b) (4) and disintegration time (less than (b) (4)). Note that the product is rapidly dissolving and desmopressin is highly soluble throughout the physiological range. A dissolution test was therefore considered unnecessary.

Three degradation products have been identified and qualified (see Unireview Section 5, Nonclinical Pharmacology / Toxicology). [Gly⁹-OH]desmopressin, [Asp⁵]desmopressin, and [Gln⁴]desmopressin are limited to not more than (b) (4) %, respectively. Unidentified impurities are limited to not more than (b) (4) %, and total degradation products are limited to not more than (b) (4) %.

Stability data support an expiration dating period of 48 months at 25°C when stored the original foil-foil blister packaging, which protects the product from both moisture and light.

The first desmopressin acetate-containing product was a nasal solution approved in 1978. In addition to the nasal solution, desmopressin acetate is available as a metered nasal spray, tablets, and an injection. The proposed sublingual tablet may offer a more convenient dosage form for some patients.

B. Quality Assessment Overview

NDA 22517 was initially submitted on June 22, 2009. Three strengths of Desmopressin Orally Disintegrating Tablets (also referred to as Desmopressin Melt) were described: 25 mcg, 50 mcg and 100 mcg desmopressin (as the free base). The application was recommended for approval from the chemistry, manufacturing and controls (CMC) perspective (see Memo dated April 19, 2010). However, the Office of Compliance had not made an overall CGMP recommendation and labeling had not been finalized. A Complete Response Letter was issued at the end of the first review cycle (April 22, 2010) due to clinical/statistical, clinical pharmacology and nonclinical deficiencies. The application subsequently received two additional Complete Response Letters due to ongoing clinical issues. No significant CMC changes have been made since the original submission.

Drug Substance: The chemistry, manufacturing and controls for desmopressin acetate as synthesized by PolyPeptide Laboratories (PPL; Sweden) are documented in PPL's Type II DMF 8396. Additional supporting information is provided in the NDA. The drug substance CMC information was reviewed during the previous three review cycles, and was found adequate. Updated CMC information submitted to the DMF and to the NDA continues to support the use of desmopressin acetate manufactured by PPL in the manufacture of Nodurna sublingual tablets. See the attached Drug Substance Review by Dr. Joseph Leginus for details.

Drug Product: Drug product CMC is essentially unchanged since first submitted in 2009. The reviews completed during the previous three review cycles concluded that the information provided was adequate to support approval of the NDA.

The recent resubmission includes updated stability data from process validation batches. In addition, Ferring proposed an alternative secondary packaging site.

The updated stability data from the process validation batches continues to support an expiration dating period of 48 months when stored at 25°C in the original foil-foil blister packaging.

Ferring Production Inc. (FPI), Parsippany, NJ was introduced as an alternate secondary packaging site. FPI is also responsible for Quality Assurance release of finished drug product. See discussion under Facilities.

Based on the previous CMC reviews and recommendation, and the review of the additional information provided in this resubmission, it is concluded that Ferring has provided sufficient information to assure the identity, strength, purity, and quality of the proposed sublingual tablets.

Therefore, this resubmission is recommended for approval from the drug product perspective with a 48-month of expiration dating period. See the attached Drug Product Review by Dr. Hong Cai for details.

Environmental Analysis: Ferring has claimed a categorical exclusion in accordance with 21 CFR 25.31(b). The claim was reviewed and deemed adequate by Dr. John Hill (See CMC Review #1, October 21, 2009).

Labeling: From the CMC perspective, two significant changes to the labels and labeling are required. Ferring proposes the product title, NOCDURNA (desmopressin) orally disintegrating sublingual tablets. The dosage form proposed by Ferring, 'orally disintegrating sublingual tablet' (ODST), is incorrect. The drug product is administered by placement under the tongue, where the product disintegrates, and drug released and presumably absorbed. The dosage form is thus, 'sublingual tablet'. See USP General Chapter <1121> *Nomenclature* and the USP Nomenclature Guidelines, March 2016, referenced therein.

Desmopressin acetate is currently available as nasal solutions, metered nasal sprays, injections, and oral tablets. The strength of these products is expressed in terms of the salt, desmopressin acetate. The OPQ Office of Policy for Pharmaceutical Quality (OPPQ) Product Quality Labeling (PQL) team recommends that, for consistency with these approved products, the strength of NOCDURNA be expressed based on the acetate salt. The strengths of NOCDURNA are thus 27.7 mcg of desmopressin acetate (equivalent to 25 mcg of desmopressin) and 55.3 mcg of desmopressin acetate (equivalent to 50 mcg of desmopressin).

See the attached Labeling Review for additional comments. Package insert, and foil blister and carton labeling deficiencies have been conveyed to the applicant.

The application is not approvable until these deficiencies have been corrected.

Process: See previous reviews of the chemistry, manufacturing and controls.

Facilities: The drug substance manufacturer, PolyPeptide Laboratories (Sweden) and two associated drug substance testing laboratories have acceptable CGMP status. The drug product manufacturer, Catalent Pharma, Swindon, Wiltshire, UK, also has acceptable CMGP status. Ferring GmbH, Kiel, Germany is responsible for QC testing and dispensing of the drug substance, drug product stability testing, and Quality Assurance release of finished drug product. The facility also has acceptable CGMP status. Ferring International Center in Switzerland is responsible for secondary packaging.

Ferring Production Inc. (FPI), Parsippany, NJ was introduced as an alternate secondary packaging site. FPI is also responsible for Quality Assurance release of finished drug product. The OPQ/OPF Division of Inspectional Assessment (DIA) determined that further evaluation of Ferring Switzerland and Ferring Parsippany was not necessary.

DIA issued an overall inspection recommendation of Approve on May 22, 2018. See the attached Facilities review for details.

Biopharmaceutics: See Dr. Houda Mahayni's reviews dated January 8, 2013 and September 9, 2013, which document the acceptability of the disintegration test and acceptance criterion of 'less than (b) (4) .'

Microbiology: See Product Quality Microbiology reviews dated February 12, 2010 and January 3, 2013, as well as previous reviews of the chemistry, manufacturing and controls. The drug product specification includes tests for microbiological quality (microbial enumeration) and demonstration of the absence of *E. coli*. Testing is conducted in accordance with the current edition of the USP/NF.

Analytical Methods Verification: Not applicable. Desmopressin acetate is not a new molecular entity. The analytical procedures are straightforward and none requires further verification by OPQ's Division of Pharmaceutical Analysis (DPA) laboratory in St. Louis.

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment (see Attachment D)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

{see electronic signature page}

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (*see Chemistry Review #1, 10/21/09*)

CHAPTER IV: Labeling

CHAPTER V: Process (*see Chemistry Reviews #1 - #4*)

CHAPTER VI: Facilities

CHAPTER VII: Biopharmaceutics (*see Biopharmaceutics reviews 01/08/13 and 09/09/13*)

CHAPTER VIII: Microbiology (*see Chemistry Reviews #1 - #4*)

CHAPTER IX: Additional Quality Discipline (*Not Applicable*)

Attachment I: Final Risk Assessment / Life Cycle Management

Attachment II: List of Deficiencies for Complete Response (*see Chapter IV, Labeling*)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment and Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments
Package Integrity	<ul style="list-style-type: none"> Raw materials Process parameters Scale/equipment Site 	-*		Adequate	
Appearance	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment 	-	Process development work and manufacturing process parameter during freeze drying ensure a sublingual tablet with appropriate physical characteristics	Adequate	
Identification	<ul style="list-style-type: none"> Raw materials GMPs 	-	TLC and LC/UV; adequate GMPs	Adequate	
Desmopressin Assay	<ul style="list-style-type: none"> Process parameters Scale/equipment Site 	-	Foil-foil blister protects from light and moisture.	Adequate	
Content Uniformity	<ul style="list-style-type: none"> Process parameters Scale/equipment Site 	-	(b) (4)	Adequate	(b) (4)
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	-	Foil-foil blister protects from light and moisture. Levels of three identified degradation products adequately qualified as determined by pharm/tox review team	Adequate	
Moisture Content	<ul style="list-style-type: none"> Process parameters Scale/equipment Site 	-	(b) (4)	Adequate	
Product Performance	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	-	Disintegration testing is adequate. Less than	Adequate	
Microbial Limits	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	-	Quality of raw materials, especially of (b) (4) Microbial enumeration and absence of <i>E. coli</i>	Adequate	

* Product quality risk assessments were not routinely performed when this NDA was first submitted.

ATTACHMENT II: List of Deficiencies for Complete Response

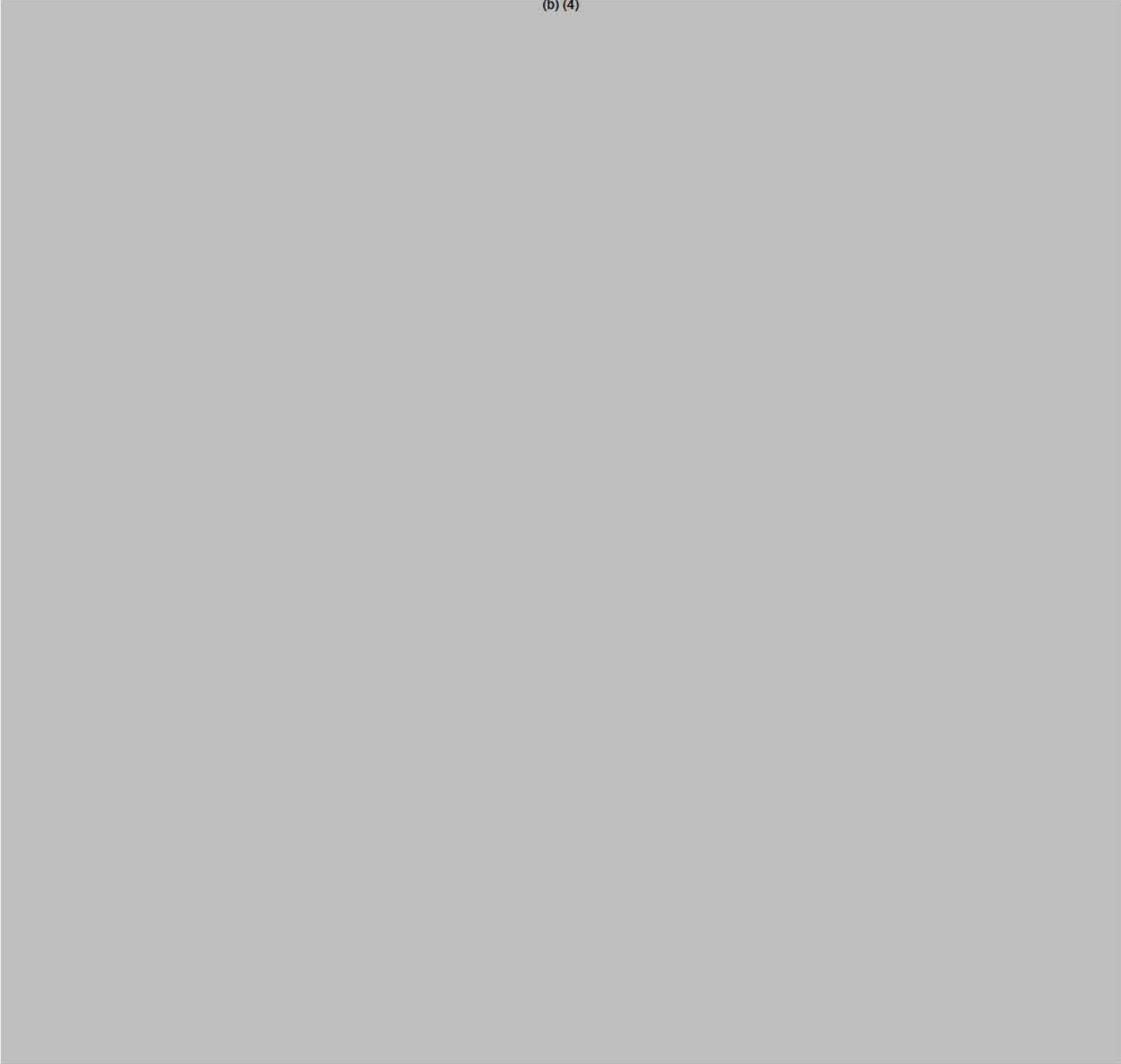
A. Regarding PI

(b) (4)



B. Regarding Labels

(b) (4)





Mark
Seggel

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LABELING

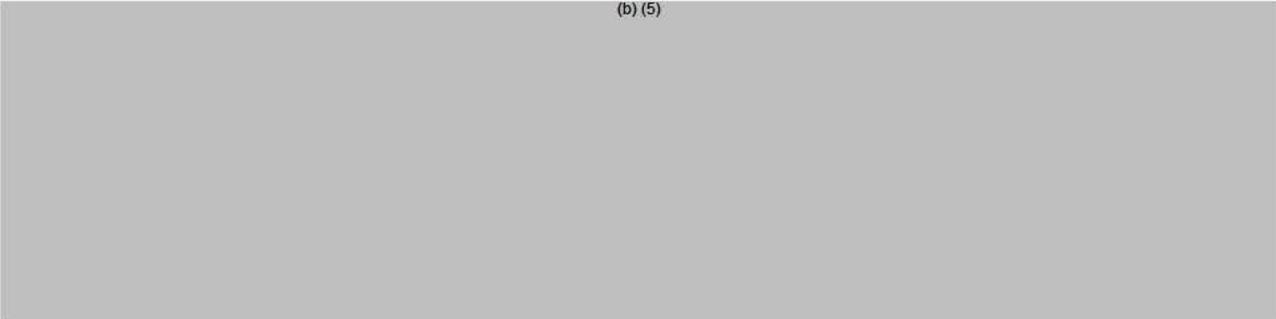
(b) (4)



2. Section 2 Dosage and Administration

Appendix:
**The recommendation regarding of the dosage form and
the Established Name by OPQ Policy.**

(b) (5)



Thanks,
Jibril



Hong
Cai

Digitally signed by Hong Cai
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GUID: 55919d6500e16bdaad5825645e4f22ff



Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/23/2018 09:37:13AM
GUID: 502d0913000029f9798ca689a802fa55

FACILITIES

[IQA Review Guide Reference](#)

NDA: 022517

Drug Product Name / Strength: NOCDURNA (desmopressin) Tablets, 25 mcg and 50 mcg

Route of Administration: Oral

Applicant Name: Ferring Pharmaceuticals Inc.

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The review of the application and inspectional documents indicate there are no significant outstanding manufacturing or facility risks that prevent approval of this application. No pre-approval inspections were requested to support the application. The manufacturing facilities listed for NDA 022517 are acceptable at this time.

List Submissions being reviewed (table):

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Seq. 0039 – (044)	12/21/2017
Seq. 0040 – (045)	01/31/2018
Seq. 0041 – (046)	02/06/2018
Seq. 0042 – (047)	02/07/2018
Seq. 0043 – (049)	03/09/2018
Seq. 0044 – (050)	03/09/2018
Seq. 0045 – (051)	04/19/2018
Seq. 0046 – (052)	04/20/2018
Seq. 0047 – (054)	05/03/2018
Seq. 0048 – (055)	05/09/2018
Seq. 0049 – (056)	05/14/2018
Seq. 0050 – (057)	05/16/2018
Seq. 0051 – (058)	05/17/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

3.2.S.2 Manufacture

(b) (4)

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Date: 6/11/2018 09:14:22AM

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BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22-517 Resubmission	Reviewer: Houda Mahayni, Ph.D.	
Submission Date:	July 17, 2013		
Division:	DMEP	Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D.	
Applicant:	Ferring Pharmaceuticals		
Trade Name:	Nocdurna™	Date Assigned:	July 18, 2013
Generic Name:	Desmopressin	Date of Review:	August 21, 2013
Indication:	Treatment of adult nocturia	Type of Submission: Resubmission of 505 (b)(2) application (Complete Response)	
Formulation/strengths:	Orally Disintegrating Tablet/ 10, 25, 50, 75, and 100 µg		
Route of Administration:	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submissions Type:		Submission Date:	
Original Submission		June 19, 2009	
First cycle Complete Response letter		April 22, 2010	
Resubmission		July 30, 2012	
Second cycle Complete Response letter		January 30, 2013	
End of Review Meeting Minutes		June 5, 2013	
Resubmission		July 17, 2013	
Cross Referenced Applications:	NDA 19-955 DDAVP® (Desmopressin acetate) Tablets by Sanofi Aventis US as the Reference Listed Drug (RLD) IND 65,890 FE992026 Desmopressin Sublingual Melt NDA 21-333 Desmopressin Acetate Nasal Spray NDA 21-795 Desmopressin Acetate Tablets DMF 8396		
Biopharmaceutics Focus:	Disintegration test		
SUMMARY OF BIOPHARMACEUTICS FINDINGS:			
<p>NOCDURNA™ contains the active ingredient Desmopressin (as the acetate), which is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The proposed indication is for treatment of nocturia in adults.</p> <p>The Applicant cross referenced NDA 19-955 DDAVP® (Desmopressin acetate) tablets by Sanofi Aventis as the Reference Listed Drug (RLD) to this NDA. The Applicant also cross referenced the following applications: IND 65,890 FE992026 Desmopressin Sublingual Melt; NDA 21-333 Desmopressin Acetate Nasal Spray; NDA 21-795 Desmopressin Acetate Tablets; and DMF 8396.</p> <p>The original submission of this NDA was submitted on June 19, 2009, pursuant to section 505 (b) (2) and FDA issued a first cycle COMPLETE RESPONSE (CR) letter on April 22, 2010. As a result, the Applicant provided a Resubmission to the NDA on July 30, 2012, addressing the issues identified in the FDA's complete response letter dated April 22, 2010. However, FDA issued a second cycle Complete Response letter on January 30, 2013 due to clinical and statistical deficiencies.</p>			

Regarding Biopharmaceutics, the proposed disintegration testing and acceptance criterion for Desmopressin ODT were found acceptable during the second review cycle of the NDA's Resubmission dated July 30, 2012.

The current third Resubmission to the NDA dated July 17, 2013, is addressing the clinical and statistical deficiencies identified in the January 30th CR letter.

RECOMMENDATION

ONDQA-Biopharmaceutics does not have any deficiencies/issues to be reviewed in the current Resubmission dated July 17, 2013, and therefore, from the Biopharmaceutics perspective, approval is recommended for NDA 22-517 for NocdurnaTM (desmopressin acetate) Orally Disintegrating Tablets.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 22-517 DARRTS, RLostritto*

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/s/

HOUDA MAHAYNI
09/09/2013

ANGELICA DORANTES
09/09/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22-517	Reviewer: Houda Mahayni, Ph.D.	
Submission Date:	July 30, 2012, and January 8, 2013		
Division:	DMEP	Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D.	
Applicant:	Ferring Pharmaceuticals		
Trade Name:	Nocdurna™	Date Assigned:	August 1, 2012, and January 8, 2013
Generic Name:	Desmopressin	Date of Review:	December 27, 2012, and January 8, 2013
Indication:	Treatment of adult nocturia	Type of Submission: Resubmission of 505 (b)(2) application (Complete Response)	
Formulation/strengths:	Orally Disintegrating Tablet/ 10, 25, 50, 75, and 100 µg		
Route of Administration:	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submissions Type:		Submission Date:	
Type B, EOP2 Meeting Minutes (IND 65,890)		June 18, 2007	
Advice/Information Request (IND 65,890)		March 11, 2009	
Original Submission		June 19, 2009	
End-of-Review Meeting Minutes (NDA 22-517)		October 14, 2010	
Complete Response letter		April 22, 2010	
Cross Referenced Applications:	NDA 19-955 DDAVP® (Desmopressin acetate) Tablets by Sanofi Aventis US as the Reference Listed Drug (RLD) IND 65,890 FE992026 Desmopressin Sublingual Melt NDA 21-333 Desmopressin Acetate Nasal Spray NDA 21-795 Desmopressin Acetate Tablets DMF 8396		
Biopharmaceutics Focus:	Disintegration Test		
SUMMARY OF BIOPHARMACEUTICS FINDINGS:			
<p>NOCDURNA™ contains the active ingredient Desmopressin (as the acetate), which is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The proposed indication is for treatment of nocturia in adults.</p> <p>The Applicant cross referenced NDA 19-955 DDAVP® (Desmopressin acetate) tablets by Sanofi Aventis as the Reference Listed Drug (RLD) to this NDA. The Applicant also cross referenced the following applications: IND 65,890 FE992026 Desmopressin Sublingual Melt; NDA 21-333 Desmopressin Acetate Nasal Spray; NDA 21-795 Desmopressin Acetate Tablets; and DMF 8396.</p> <p>The original submission of this NDA was submitted on June 19, 2009, pursuant to section 505 (b) (2), and FDA issued a COMPLET RESPONSE (CR) letter on April 22, 2010.</p> <p>FDA informed the Applicant that the 505 (b) (2) regulatory path between the DDAVP tablet (RLD) and ODT (TBM) was not fulfilled. Therefore, to bridge the DDAVP tablet (RLD) to ODT, the Applicant agreed to perform a</p>			

comparative toxicokinetic study comparing 2x200 µg DDAVP tablet and 1x240 µg ODT. Also, the CR letter included OCP request to reanalyze the BE study (CS019) PK samples with validated analytical method or to collect PK samples in future clinical trials using properly validated bioanalytical method.

This submission includes two confirmatory trials (CS40/CS41) using the 25, 50, 75, and 100 µg dosage strengths, and a four week comparative toxicology study comparing Nocdurna with the RLD, DDAVP tablets.

The Biopharmaceutics review is focused on the acceptability of the proposed disintegration test and acceptance criteria for Desmopressin ODT.

Per ICH Q6A decision tree #7, there are several criteria, based on which disintegration may be substituted for dissolution.

- a. Product containing drug substance that is highly soluble throughout the physiological range (dose/solubility volume \leq 250 mL from pH 1.2 to 6.8).
- b. Dosage form rapidly dissolving (dissolution $>$ 80 percent in 15 minutes at pH 1.2, 4.0, and 6.8).
- c. Disintegration testing is considered most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution.

The Applicant provided data to support above criteria **a** and **b**, but not **c**. However, FDA found the proposed disintegration testing and acceptance criterion for Desmopressin ODT acceptable given that the drug substance is highly soluble throughout the physiological range (dose/solubility volume \leq 250 mL from pH 1.2 to 6.8), and the drug product is rapidly dissolving (dissolution $>$ 80% in 15 minutes at pH 1.2, 4.0, and 6.8). Although the Applicant did not provide a relationship between dissolution and disintegration, both dissolution testing and disintegration testing provide similar outcome (dissolve \sim 100% in 6 minutes or disintegrate \sim in less than 3 seconds). Nevertheless, FDA communicated the following comment to the Applicant: “You did not include dissolution testing as a quality control test of your drug product. Per SUPAC-IR guidance if changes are made post approval, they should be supported with comparative dissolution profiles and f2 similarity factor data.”

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 22-517 for Desmopressin Orally Disintegrating Tablet (25 µg and 50 µg) is recommended for APPROVAL.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 22-517 DARRTS, RLostritto*

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Submission: Demopressin orally disintegrating tablet (ODT) (60, 120, and 240µg) was approved in February 2005, as Desmopressin melt. Desmopressin ODT is a freeze-dried formulation that disintegrates instantly once placed under the tongue. It was developed in five lower strengths: 10, 25, 50, 75 and 100 µg. However, the Applicant plans to market only two lower strengths (25 and 50 µg).

The initial submission included one bioavailability (BA) study (**FE992026 CS004**) in healthy male volunteers with Desmopressin melt over the dose range 200, 400 and 800 µg, one relative BA study (**FE992026 CS020**) in healthy male and female volunteers with 240 µg Desmopressin melt, and one bioequivalence (BE) study comparing Desmopressin melt (240 µg) and Desmopressin tablets (Minirin®) (400 µg) (**FE992026 CS019**). All these studies were reviewed by OCP. The Applicant used (b) (4) for the analysis of plasma samples in these studies. However, the assay was rejected by FDA. The Applicant requested a biowaiver to conduct pharmacokinetics (PK) studies on the proposed lower dosage strengths (10, 25, 50, and 100 µg) at the IND stage (IND 65,890) because the assay was below the detection limits for Desmopressin at proposed lower doses, and FDA granted the waiver on March 11, 2009.

Review: The Biopharmaceutics review is focused on the acceptability of the proposed disintegration test and acceptance criteria for Desmopressin ODT.

Drug Substance

The drug substance of Desmopressin ODT 25, 50, 75 and 100 µg is Desmopressin acetate and is identical to the drug substance used in the commercially available Desmopressin tablet and in Desmopressin ODT 60, 120 and 240 µg.

Drug Product

Desmopressin ODT is a freeze dried orally disintegrating tablet which is designed to disperse rapidly in the mouth. The dosage form can be taken without water.

The development of the proposed Desmopressin ODT in the following strengths: 25, 50, 75, and 100 µg was based on the already existing commercially available, Desmopressin ODT 60, 120 and 240 µg. All strengths have identical composition with the exception of the Desmopressin content. During product development, the dosage form was referred as melt, a lyophilisate, a wafer, an orodispersible tablet, or an orally disintegrating tablet. In this submission, the term “melt” is synonymous with the orally disintegrating tablet used in the Phase 3 trials.

The proposed dose strengths for commercialization of Desmopressin orally disintegrating tablet are 25 µg and 50 µg. The composition of each strength is shown in Table 1 and Table 2, respectively.

Table 1: Composition of Desmopressin orally disintegrating tablet 25 µg

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph. Eur./USP Curr. Ed.
Gelatin	(b) (4)		Ph. Eur./USP/JP, Curr. Ed.
Mannitol			Ph. Eur./USP/JP, Curr. Ed.
Citric acid, anhydrous			Ph. Eur./USP/JP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

Table 2: Composition of Desmopressin orally disintegrating tablet 50 µg

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.050 mg	Drug Substance	Ph. Eur./USP Curr. Ed.
Gelatin	(b) (4)		Ph. Eur./USP/JP, Curr. Ed.
Mannitol			Ph. Eur./USP/JP, Curr. Ed.
Citric acid, anhydrous			Ph. Eur./USP/JP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 50 µg desmopressin free base.

The composition of the approved dose strengths 60, 120 and 240 µg are shown in Table 3

Table 3: Composition of Marketed Strengths Desmopressin ODT

Component	60 µg	120 µg	240 µg
Desmopressin (µg)	60	120	240
Gelatin (mg)		(b) (4)	
Mannitol (mg)			
Citric acid, anhydrous		(b) (4)	

Among the physical properties studied of Desmopressin ODT is the disintegration time.

Disintegration Testing

Desmopressin ODT is a freeze dried orally disintegrating tablet designed to disperse rapidly in the mouth.

A disintegration test was performed to control the release of the drug substance from the drug product. The Applicant stated that per ICH Q6A guideline, for rapidly dissolving products (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) containing drugs which are highly soluble throughout the physiological range, dissolution may be replaced by disintegration.

The Applicant submitted solubility data of Desmopressin drug substance at 37°C in aqueous solutions from pH 1.2 to pH 7.6. The data showed that the highest dose strength (50 µg) is soluble in < 250 mL aqueous media over the pH range of 1-7.5. The final concentration of 50 µg Desmopressin in 250 mL is 0.2 µg/mL. Table 4 shows the list of buffer solutions used to assess the solubility of Desmopressin drug substance (batch 112137-01) in a water bath kept at 37°C for 30 minutes with a mixing step after 15 minutes.

A sample solution contains 0.2 mg/mL (a Desmopressin concentration 1000 times higher than the highest dose strength in 250 mL) is tested. The Applicant reported that the samples are analyzed using a validated stability indicating reversed phase high performance liquid chromatography method with UV detection at 220 nm. The Applicant did not submit the method for review, as it is submitted in DMF 8396.

Table 4: List of buffer solutions used for pH 1 to pH 7.6

Target pH value	Buffer solution	Measured pH value of buffer solution
pH 1.2*	0.085 M HCl in 0.05 M KCl	pH 1.1
pH 2.0*	0.013 M HCl in 0.05 M KCl	pH 1.9
pH 4.0	0.050 acetate buffer (AcOH/NaAc)	pH 4.0
pH 6.0*	0.050 M phosphate buffer (KH ₂ PO ₄ /NaOH)	pH 6.0
pH 7.6*	0.050 M phosphate buffer (KH ₂ PO ₄ /NaOH)	pH 7.6

*) buffer solution prepared according to USP

The recovery of Desmopressin is listed in Table 5. The amount dissolved is in the range of 98% to 101% with RSD less than 1.9%. The Applicant reported that Desmopressin can be classified as highly soluble substance since the highest dose strength is soluble in < 250 mL of aqueous media over the pH range of 1-7.5.

Table 5: Dissolved amount of drug substance at pH 1 to pH 7.6

Targeted pH value	Recovery of desmopressin after 30 minutes at 37°C (%)	RSD (%)	Measured pH value of desmopressin buffer solution after 30 minutes at 37°C
pH 1.2	98	1.9	1.1
pH 2.0	101	0.2	1.9
pH 4.0	101	1.2	4.0
pH 6.0	101	0.9	6.0
pH 7.6	101	1.1	7.6

The Applicant submitted under IND 65,890 comparative dissolution data in three media (pH 1.2, 4.0, and 6.8) to compare the proposed strengths (10, 25, 50, and 100 µg) and the marketed strengths (60, 120, and 240 µg). Table 6 shows the dissolution results of the proposed strengths and Table 7 shows the dissolution results of the marketed strengths. In both cases the dissolution is approximately 100 % after 6 minutes under all pH media tested.

Table 6: Dissolution Results for the Proposed Strengths (10, 25, 50, and 100 µg)

Strength (µg)	pH of dissolution medium	% dissolution after 6 min (n=12)	% dissolution after 12 min (n=12)
10	1.2	103	103
10	4.0	101	101
10	6.8	99	100
25	1.2	103	104
25	4.0	100	101
25	6.8	100	98
50	1.2	102	104
50	4.0	99	100
50	6.8	101	102
100	1.2	97	98
100	4.0	101	101
100	6.8	99	101

Table7: Dissolution Results for the Marketed Strengths (60, 120, and 240 µg)

Strength (µg)	pH of dissolution medium	% dissolution after 6 min (n=12)	% dissolution after 12 min (n=12)
60	1.2	99	103
60	4.0	101	101
60	6.8	99	100
120	1.2	109	110
120	4.0	107	108
120	6.8	104	104
240	1.2	101	102
240	4.0	103	104
240	6.8	100	102

For quality control, the Applicant proposed disintegration testing instead of dissolution testing. The Applicant proposed disintegration testing in 37°C water as disintegration media, and the disintegration time to be determined on the slowest disintegrating unit of 5. The proposed acceptance criterion for Desmopressin ODT is less than (b) (4). The Applicant reported the disintegration result of stability data of both dosage strengths (25 and 50 µg) under long term and accelerated storage conditions to be less than 3 seconds.

Reviewer's Comment:

The disintegration testing is acceptable for Desmopressin ODT given that the drug substance is highly soluble throughout the physiological range (dose/solubility volume ≤ 250 mL from pH 1.2 to 6.8), and the drug product is rapidly dissolving (dissolution > 80% in 15 minutes at pH 1.2, 4.0, and 6.8). Although the Applicant did not provide a relationship between dissolution and disintegration, both dissolution testing and disintegration testing provide similar outcome (dissolve ~ 100% in 6 minutes or disintegrate ~ in less than 3 seconds). Therefore, the proposed disintegration test and acceptance criterion for Desmopressin ODT (NMT (b) (4)) are found acceptable. Nevertheless, FDA communicated the following comment to the Applicant: “You did not include dissolution testing as a quality control test of your drug product. Per SUPAC-IR guidance if changes are made post approval, they should be supported with comparative dissolution profiles and f2 similarity factor data.”

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/s/

HOUDA MAHAYNI
01/08/2013

ANGELICA DORANTES
01/08/2013



NDA 22-517

Nocdurna (Desmopressin) Orally Desintegrating Sublingual Tablets

Ferring Pharmaceuticals Inc.

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

Chemistry Review Data Sheet

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. **NDA:** 22-517
2. **Review:** 4
3. **Review Date:** 07-Jan-2013
4. **Reviewer:** Xavier Ysem, PhD

5. Previous Documents:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission (SN 0000)	22-Jun-2009
Amendment (SN 0006) <i>Response to CMC filing deficiencies</i>	24-Sep-2009
Amendment (SN 0009) <i>Response to CMC filing deficiencies</i>	22-Dec-2009
Amendment (SN 0010) <i>Labeling</i>	14-Jan-2010

6. Submission(S) Being Reviewed:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (SN 0017) <i>Complete Response Resubmission Class 2</i>	30-Jul-2012
Amendment (SN 0021) <i>Quality/ Response to Information Request</i>	12-Oct-2012
Amendment (SN 0022) <i>Quality/ Response to Information Request</i>	26-Oct-2012

7. Name & Address of Applicant:

Name: Ferring Pharmaceuticals Inc.
Address: 4 Gatehall Drive 3rd Floor
Parsippany, New Jersey 07054
Representative: John C. Kim, RPh, JD
Senior Director of Regulatory Affairs
Telephone: (973) 796-1730

8. Drug Product Name/Code/Type:

- a) Proprietary Name: Nocdurna™ [(desmopressin) Oral Disintegrating Sublingual Tablets]
Proprietary name granted 25-Oct-2012
b) Non-Proprietary Name (USAN): Desmopressin Acetate
c) Code Name/# (ONDC only): Desmopressin Melt
d) Chem. Type/Submission Priority (ONDC only):
· Chem. Type: 3
· Submission Priority: S

9. **Legal Basis For Submission:** 505(b)(2)

10. **Pharmacol. Category:** Treatment of nocturia in adults

11. **Dosage Form:** Tablet (Orally Disintegrating Sublingual)

12. **Strength/Potency:** 25 and 50 µg

13. **Route of Administration:** Sublingual

The Chemistry Review for NDA 22-517

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- From the Chemistry, Manufacturing and Control (CMC) point of view, this NDA is recommended for APPROVAL.
- Based on the provided stability data a 48 month expiry period is granted.

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

None

II. Summary of Chemistry Assessments

The original submission, SN 0000, contained information on the 25, 50, and 100 µg doses and proposed to market only the 25 and 100 µg doses. In the complete response submission, SN 0017, the 100 µg dose is withdrawn and Ferring proposes to only market the 25 µg and 50 µg doses. The manufacturing process of the 50 µg dose and its site of manufacture are the same as those described in the original submission for the other doses. The Catalent UK Packaging Limited, Corby, UK, as a secondary packaging site is removed, and the Ferring International Center, SA, Switzerland, is added as the secondary packaging site. Validation of Analytical test procedure for identification, content and degradation products is updated.

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

- Drug Substance *Desmopressin Acetate*

Desmopressin is a synthetic analog of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprise a desamination of the N-terminal and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin belongs to the pharmacologic class of posterior pituitary hormone.

The molecular weight of desmopressin (as the acetate) is 1183.84 g/mole and the molecular formula is $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. Desmopressin acetate bulk drug substance is produced as a lyophilized powder and consequently amorphous.

The synthesis and purification of this peptide is covered under DMF 8396. This DMF has been reviewed and is current; there are no outstanding CMC issues.

- Drug Product *Nocturna™ (desmopressin) Tablets*

Nocturna is formulated as an orally disintegrating tablet and supplied in two dosage strengths: 25 and 50 µg (mcg) of desmopressin (as the free base). Nocturna contains the active ingredient desmopressin (as desmopressin acetate) and the following excipients: gelatin (derived from fish), mannitol and citric acid. Tablet strengths are differentiated by the debossing (Nocturna 25 µg: White, round, orally disintegrating tablet with "25" on one side; Nocturna 50 µg: White, round, orally disintegrating tablet with "50" on one side).

These ingredients are

(b) (4)

to yield the final tablets. The

tablets are packaged in an (b) (4) blister in (b) (4) a 10 count patient package:

Nocdurna 25 µg: NDC 55566-5050-01 3 x 10 Unit Dose Blister Box of 30

Nocdurna 50 µg: NDC 55566-5052-01 3 x 10 Unit Dose Blister Box of 30

(b) (4)

The quality of the Nocdurna drug product is assured by visual inspection of the tablets, HPLC purity and impurity analysis, disintegration time, uniformity of mass, and microbiological quality.

Real-time, long-term stability data have been provided in the NDA which indicate that the drug product is stable for up to 48 months. Data have been provided which demonstrate that the Nocdurna drug product is sensitive to light. Based on these data, as requested by the Applicant, an expiry period of 48 months is granted when stored at 25 ± 2 °C/ 60 ± 5 % RH, and protected from light. The storage statement to be included in the PI is noted as follows: (b) (4) excursions permitted to 15 – 30 °C (50 – 86 °F). Keep in original package to protect from moisture and light. Use immediately upon opening individual tablet blister.”

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

Nocdurna is intended to be administered sublingually without water, one hour before bedtime (women: 25 µg; men: 50 µg).

The proposed indication is for treatment of nocturia in adults. Nocdurna works by acting on in the collecting duct of the kidneys by increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application.

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Review Chemist/ ONDQA/ DNDQA III/ Branch VII 07-Jan-2012

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief/ ONDQA/ DNDQA III/ Branch VII 07-Jan-2012

C. CC Block

Jennifer Johnson Project Manager/ OND/ ODEII/DMEP

Chemistry Assessment**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data**

See CMC Reviews #1, 2, and 3.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1**C. Establishment Inspections** *Satisfactory*

Polypeptide Laboratories AB's (PPL) facility in Limhamn, Sweden, which is involved in the manufacture, testing and packaging of the drug substance, has been evaluated and found acceptable by the Office of Compliance (pending issue satisfactorily resolved). All facilities involved in the manufacture, testing and packaging of the drug substance and drug product requested for inspection have been found acceptable by the Office of Compliance (acceptable overall recommendation given on December 27, 2012). The EER Summary Report, dated 07-Jan-2013, is attached.

Attached

	<u>Page</u>
EER Summary Report dated 07-Jan-2013 (3 pages)	11

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 22517/000	Sponsor:	FERRING PHARMS
Org. Code:	510		4 GATEHALL DR 3RD FL
Priority:	5S		PARSIPPANY, NJ 07054
Stamp Date:	22-JUN-2009	Brand Name:	NOC DURNA
P D U F A Date:	30-JAN-2013	Estab. Name:	
Action Goal:		Generic Name:	DESMOPRESSIN
District Goal:	01-DEC-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; TABLET, ORALLY DISINTEGRATING; DESMOPRESSIN; 25UGM
			002; TABLET, ORALLY DISINTEGRATING; DESMOPRESSIN; 100UGM
FDA Contacts:	J. JOHNSON	Project Manager	(HFD-510) 3017962194
	X. YSERN	Review Chemist	3017961779
	S. TRAN	Team Leader	3017961764

Overall Recommendation:	ACCEPTABLE	on 27-DEC-2012	by R. SAFAAJAZI	0	3017964463
	PENDING	on 01-NOV-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	ACCEPTABLE	on 14-APR-2010	by JOHNSONE		

Establishment:	CFN:	FEI:	3004097791
	CATALENT PHARMASOLUTIONS SEEDGE CLOSE		
	CORBY, NORTHANTS, , UNITED KINGDOM		
DMF No:		AA DA:	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	QA I Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN:	FEI:	3003812585
	CATALENT UK SWINDON ZYDIS LIMITED FRANKLAND ROAD, BLAGROVE		
	SWINDON, WILTSHIRE, , UNITED KINGDOM		
DMF No:		AA DA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	QA I Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

(b) (4)



Establishment:	CFN: 9611638	FEI: 3002806979	
	FERRING GMBH WITTLAND 11 KIEL, SCHLESWIG-HOLSTEIN, GERMANY		
DMF No:			AA DA:
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN:	FEI: 3005724652	
	FERRING INTERNATIONAL CENTER S.A. CHEMIN DE LA VERGOGNAUSAZ 50 ST-PREX, SWITZERLAND		
DMF No:			AA DA:
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	01-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		



FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 9615997 FEI: 3002807004
POLYPEPTIDE LABORATORIES (SWEDEN) AB
HÖGERUDSGATAN 21, LIMHAMN
LIMHAMN, SWEDEN
DMF No: 8396 AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-DEC-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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/s/

XAVIER J YSERN
01/07/2013

ALI H AL HAKIM
01/07/2013

Product Quality Microbiology Review

03 January 2013

NDA: 22-517/N-000

Drug Product Name

Proprietary: Nocdurna
Non-proprietary: Desmopressin

Review Number: 2.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 JUL 2012	30 JUL 2012	31 JUL 2012	02 AUG 2012
12 OCT 2012	12 OCT 2012	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
19 JUN 2009	1	12 FEB 2010

Applicant/Sponsor

Name: Ferring Pharmaceuticals, Inc.
Address: 4 Gatehall Dr.
Third Floor
Parsippany, NJ 07054
Representative: John Kim
Telephone: 973-796-1730

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** 505(b)(2) NDA (resubmission).
 - 2. SUBMISSION PROVIDES FOR:** Marketing authorization.
 - 3. MANUFACTURING SITE:**
Catalent UK Swindon Zydis Limited
Frankland Rd.
Blagrove, Swindon
Wiltshire, SN5 8RU
United Kingdom
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Orally Disintegrating Tablets.
 - Oral Ingestion.
 - 25 µg and 50 µg.
 - 5. METHOD(S) OF STERILIZATION:** The subject drug product is not sterile.
 - 6. PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated for the treatment of nocturia in adults.
- B. SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review #1 of NDA 22-517/N-000; dated 12 February 2010
- C. REMARKS:**
The NDA is submitted electronically in the eCTD format.

File Name: N022517R2.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 22-517/N-000 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - ^{(b) (4)}



- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. **Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS
- B. **Endorsement Block** _____
Bryan S. Riley, Ph.D.
Senior Microbiology Reviewer
Acting Team Leader
CDER/OPS/NDMS
- C. **CC Block**
N/A

Product Quality Microbiology Assessment

Reference is made to Microbiology Review #1 of NDA 22-517/N-000 (dated 12 February 2010) which recommended approval of the subject NDA from the perspective of product quality microbiology. At that time, CDER allowed microbial limits skip lot testing for tablet products. Currently, CDER no longer allows firms to perform skip lot testing.

On 19 September 2012, the OND Project Manager forwarded the following Microbiology Information Request to the applicant.

A microbiology review of NDA 22-517 is in progress. Following is a comment and request for additional information:

Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b).

As an alternative to skip lot testing, applicants may propose to omit finished product microbial limits testing for batch release and substitute in-process manufacturing controls, tests and acceptance criteria that provide assurance of the microbiological quality for each batch of product. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:

- Microbial limits data for critical raw materials,*
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and*
- In-process control parameters (e.g., heat, drying, washing) that may affect product quality microbiology.*

In addition, microbial limits testing should be performed at the initial time point (at a minimum) on stability samples.

- In lieu of testing each finished product batch for microbial limits, remove the reference to microbiological quality tests from the drug product release specifications.*
- Since your current stability protocol includes microbiological testing at initial time, 12, 24, 26 and 48 months; you need NOT modify the drug product stability specification.*

The applicant provided a response to this Information Request on 12 October 2012. The applicant will test each batch of drug product for microbial limits. Table 1 (copied from Table 3.2.P.5.1 of the amendment) summarizes the microbiological testing that will be performed on each product batch.

Table 1. Microbiological Testing at Product Release

Test	Analytical principle	Reference to analytical procedure	Acceptance criteria Shelf life
Microbiological quality:			
Total aerobic microbial count (TAMC)	Microbial enumeration	Ph.Eur./USP;Curr.Ed	(b) (4)
Total yeasts and moulds count (TYMC)	Microbial enumeration	Ph.Eur./USP;Curr.Ed	
Absence of <i>E. coli</i>	Selective media	Ph.Eur./USP;Curr.Ed	

Satisfactory

Reviewer's Comment

1. As described in Microbiology Review #1 of the subject NDA, "The applicant carried out verification studies to demonstrate that the stated microbial limits testing methods are suitable for use with the subject drug product. These studies were documented in Summary Reports PR 182111 and PR 182113. "
2. The applicant has met regulatory expectations regarding testing for microbiological quality at product release.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There are no microbiology deficiencies identified.

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/s/

JOHN W METCALFE
01/03/2013

BRYAN S RILEY
01/03/2013
I concur.



NDA 22-517

Nocdurna (Desmopressin) Orally Desintegrating Sublingual Tablets

Ferring Pharmaceuticals Inc.

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

Chemistry Review Data Sheet

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. **NDA:** 22-517
2. **Review:** 3
3. **Review Date:** 06-Dec-2012
4. **Reviewer:** Xavier Ysem, PhD

5. Previous Documents:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission (SN 0000)	22-Jun-2009
Amendment (SN 0006) <i>Response to CMC filing deficiencies</i>	24-Sep-2009
Amendment (SN 0009) <i>Response to CMC filing deficiencies</i>	22-Dec-2009
Amendment (SN 0010) <i>Labeling</i>	14-Jan-2010

6. Submission(S) Being Reviewed:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (SN 0017) <i>Complete Response Resubmission Class 2</i>	30-Jul-2012
Amendment (SN 0021) <i>Quality/ Response to Information Request</i>	12-Oct-2012
Amendment (SN 0022) <i>Quality/ Response to Information Request</i>	26-Oct-2012

7. Name & Address of Applicant:

Name: Ferring Pharmaceuticals Inc.
Address: 4 Gatehall Drive 3rd Floor
Parsippany, New Jersey 07054

Representative: John C. Kim, RPh, JD
Senior Director of Regulatory Affairs

Telephone: (973) 796-1730

8. Drug Product Name/Code/Type:

- a) Proprietary Name: Nocdurna™ [(desmopressin) Oral Disintegrating Sublingual Tablets]
Proprietary name granted 25-Oct-2012
- b) Non-Proprietary Name (USAN): Desmopressin Acetate
- c) Code Name/# (ONDC only): Desmopressin Melt
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. **Legal Basis For Submission:** 505(b)(2)

10. **Pharmacol. Category:** Treatment of nocturia in adults

11. **Dosage Form:** Tablet (Orally Disintegrating Sublingual)

12. **Strength/Potency:** 25 and 50 µg

13. **Route of Administration:** Sublingual

The Chemistry Review for NDA 22-517

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- From the Chemistry, Manufacturing and Control (CMC) point of view, this NDA is recommended for APPROVAL.
- The overall CGMP evaluation/recommendation through the Office of Compliance remains outstanding.
- Based on the provided stability data a 48 month expiry period is granted.

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

None

II. Summary of Chemistry Assessments

The original submission, SN 0000, contained information on the 25, 50, and 100 µg doses and proposed to market only the 25 and 100 µg doses. In the complete response submission, SN 0017, the 100 µg dose is withdrawn and Ferring proposes to only market the 25 µg and 50 µg doses. The manufacturing process of the 50 µg dose and its site of manufacture are the same as those described in the original submission for the other doses. The Catalent UK Packaging Limited, Corby, UK, as a secondary packaging site is removed, and the Ferring International Center, SA, Switzerland, is added as the secondary packaging site. Validation of Analytical test procedure for identification, content and degradation products is updated.

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

- Drug Substance *Desmopressin Acetate*

Desmopressin is a synthetic analog of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprise a desamination of the N-terminal and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin belongs to the pharmacologic class of posterior pituitary hormone.

The molecular weight of desmopressin (as the acetate) is 1183.84 g/mole and the molecular formula is $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. Desmopressin acetate bulk drug substance is produced as a lyophilized powder and consequently amorphous.

The synthesis and purification of this peptide is covered under DMF 8396. This DMF has been reviewed and is current; there are no outstanding CMC issues.

- Drug Product *Nocturna™ (desmopressin) Tablets*

Nocturna is formulated as an orally disintegrating tablet and supplied in two dosage strengths: 25 and 50 µg (mcg) of desmopressin (as the free base). Nocturna contains the active ingredient desmopressin (as desmopressin acetate) and the following excipients: gelatin (derived from fish), mannitol and citric acid. Tablet strengths are differentiated by the debossing (Nocturna 25 µg: White, round, orally disintegrating tablet with "25" on one side; Nocturna 50 µg: White, round, orally disintegrating tablet with "50" on one side).

These ingredients are (b) (4). The tablets are packaged in an (b) (4) blister in (b) (4) a 10 count patient package:

Nocdurna 25 µg: NDC 55566-5050-01 3 x 10 Unit Dose Blister Box of 30

Nocdurna 50 µg: NDC 55566-5052-01 3 x 10 Unit Dose Blister Box of 30

(b) (4)

The quality of the Nocdurna drug product is assured by visual inspection of the tablets, HPLC purity and impurity analysis, disintegration time, uniformity of mass, and microbiological quality.

Real-time, long-term stability data have been provided in the NDA which indicate that the drug product is stable for up to 48 months. Data have been provided which demonstrate that the Nocdurna drug product is sensitive to light. Based on these data, as requested by the Applicant, an expiry period of 48 months is granted when stored at 25 ± 2 °C/60 ± 5 % RH, and protected from light. The storage statement to be included in the PI is noted as follows: (b) (4) excursions permitted to 15 – 30 °C (50 – 86 °F). Keep in original package to protect from moisture and light. Use immediately upon opening individual tablet blister.”

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

Nocdurna is intended to be administered sublingually without water, one hour before bedtime (women: 25 µg; men: 50 µg).

The proposed indication is for treatment of nocturia in adults. Nocdurna works by acting on in the collecting duct of the kidneys by increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application.

III. Administrative

A. Reviewer's Signature

Xavier Ysem, PhD Review Chemist/ ONDQA/ DNDQA III/ Branch VII 04-Dec-2012

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief/ ONDQA/ DNDQA III/ Branch VII 04-Dec-2012

C. CC Block

Jennifer Johnson Project Manager/ OND/ ODEII/DMEP

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/s/

XAVIER J YSERN
12/07/2012

ALI H AL HAKIM
12/07/2012



Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: 19-APR-2010

FROM: John C. Hill, Ph.D., CMC Reviewer

THROUGH: Prasad Peri, Ph.D., Acting Chief, DPA-I

TO: Johnson, Jennifer, Regulatory Project Manager
File, NDA 22-517

SUBJECT: **Establishment Evaluation**

The establishment inspection was not completed at the time when either the primary or the secondary chemistry review of NDA 22-517 was signed-off in DARRTS.

The EER (Establishment Evaluation Report) has since been issued; the listed facilities were found to be acceptable and an overall recommendation of "ACCEPTABLE" was issued on 14-APR-2010.

Overall, NDA 22-517 is recommended for approval from the standpoint of chemistry, manufacturing and controls.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

JOHN C HILL
04/19/2010

PRASAD PERI
04/19/2010
I concur

Nocdurna (desmopressin) Orally Disintegrating Tablet NDA 22-517

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Ferring Pharmaceuticals
4 Gatehall Drive, Third Floor,
Parsippany, NJ 07054

Representative: Ronald T. Hargreaves, Ph.D., Director Regulatory Affairs
Phone: 973-769-1730

Indication: Treatment of nocturia in adults.

Presentations:

NOCDURNA 25 mcg: White, round, orally disintegrating tablet with "25" on one side.
NDC 55566-5050-01 3 x 10 Unit Dose Blister Box of 30

(b) (4)

(b) (4)

EER Status: Recommendation pending

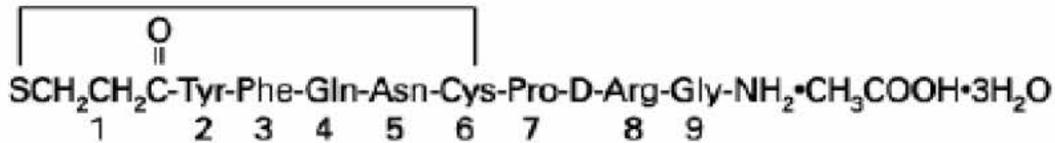
Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology –Acceptable

Original Submission: 22-JUN-2009

Post-Approval CMC Commitments: None

Drug Substance:

Desmopressin is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprise a desamination of the N-terminal and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin belongs to the pharmacologic class of posterior pituitary hormone. The API works by acting in the collecting duct of the kidneys, increasing urine concentration and decreasing urine production, which in turns leads to a decrease in voiding frequency. Desmopressin acetate bulk drug substance is produced as a lyophilized powder and is amorphous. The molecular weight of desmopressin (as the acetate) is 1183.84 g/mole and the molecular formula is $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. The structure is indicated below:



The synthesis and purification of this peptide is covered under DMF 8396. This DMF has been reviewed and is current; there are no outstanding CMC issues.

The drug substance is synthetically manufactured and tested by Polypeptide Laboratories (Sweden) AB, the holder of DMF 8396.

The drug substance quality is controlled by testing for the following attributes: Appearance, ID, HPLC, Amino acid analysis, Specific optical rotation, Peptide content, (b) (4) content, Water content, Peptide related impurities (HPLC), Total impurities, Residual (w) (4), Microbial limits, and Bacterial endotoxins.

Conclusion: The drug substance is satisfactory.

Drug Product:

Nocdurna is formulated as an orally disintegrating tablet and supplied in two dosage strengths: 25 and 100 mcg of desmopressin (as the free base). Nocdurna contains the active ingredient desmopressin acetate trihydrate and the following excipients: gelatin (derived from fish), mannitol and citric acid. These ingredients are (b) (4) to yield the final tablets. The tablets are packaged in an (b) (4) blister in (b) (4) a 10 count patient package.

The quality of the Nocdurna drug product is assured by visual inspection of the tablets, HPLC purity and impurity analysis, disintegration time, uniformity of mass and microbiological quality.

The drug product is manufactured and tested by Catalent UK Swindon Zydis Limited, in the UK.

Conclusion: The drug product is satisfactory.

Outstanding issues: EES. Acceptable compliance status has **NOT** been provided

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:

From a CMC perspective, **the application is recommended for approval, pending an acceptable recommendation from the Office of Compliance for the manufacturing and testing facilities.**

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22517

ORIG-1

FERRING
PHARMACEUTICA
LS INC

NOCDURNA

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/s/

PRASAD PERI
03/23/2010

NDA 22-517

Nocdurna (desmopressin) Orally Disintegrating Tablet

Ferring Pharmaceuticals Inc.

Chemistry Review #2

John C. Hill, Ph.D.
ONDQA/DPMA-1 and OND/ODE II/DMEP

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Chemistry Review Data Sheet

1. NDA 22-517
2. REVIEW #:2
3. REVIEW DATE: 02-MAR-2010
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 65,890
22-517 (Original NDA Application)
Responses to CMC filing deficiencies

Document Date

FE992026 (desmopressin melt)
22-JUN-2009
24-SEP-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Responses to CMC DR deficiencies
Labeling Supplement

Document Date

22-DEC-2009
14-JAN-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals
Address:	4 Gatehall Drive Third Floor Parsippany, NJ 07054
Representative:	Ronald T. Hargreaves, Ph.D., Director Regulatory Affairs
Telephone:	973-769-1730

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Nocdurna
b) Non-Proprietary Name (USAN): Desmopressin acetate
c) Code Name/# (ONDC only): Desmopressin Melt
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

LISTED REFERENCE: sanofi-aventis, DDAVP (desmopressin acetate) tablets

10. PHARMACOL. CATEGORY: Treatment of nocturina in adults

11. DOSAGE FORM: Orally Disintegrating Tablet (OTD)

12. STRENGTH/POTENCY: 25 and 100 mg strengths

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

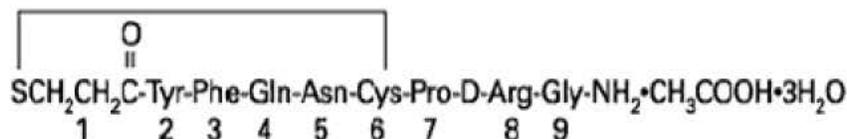
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Established Name: desmopressin acetate

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

Structural Formula:

Chemistry Review Data Sheet


17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
8396	II	PolyPeptide Laboratories (Sweden) AB	Desmopressin	1,4	Adequate	18-AUG-2009	Update review of DMF

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,890	FE992026 (desmopressin melt)
NDA	19-955	DDAVP tablets
NDA	21-333	Minirin Nasal Spray
NDA	21-798	Desmopressin acetate tablets
DMF	8396	Poly-Peptides Laboratories AB: Desmopressin acetate drug substance

18. STATUS:
ONDC:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	01-MAR-2010	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Methods Validation	Adequate/Not required	28-SEP-2009	John Hill
EA	Adequate	28-SEP-2009	John Hill
Microbiology	Adequate	12-FEB-2010	John Metcalfe

The Chemistry Review for NDA 22-517

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- From the Chemistry, Manufacturing and Control (CMC) point of view, this NDA can be approved.
- The overall CGMP evaluation/recommendation through the Office of Compliance remains outstanding.
- Based on the provided stability data a 24 month expiry period is granted. This expiry period may be extended via the annual report out to 36 months, following the approved stability protocol.

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

None

II. Summary of Chemistry Assessments

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

Drug Product

Nocdurna is formulated as an orally disintegrating tablet and supplied in two dosage strengths: 25 and 100 mcg of desmopressin (as the free base). Nocdurna contains the active ingredient desmopressin (as the free base) and the following excipients: gelatin (derived from fish), mannitol and citric acid. These ingredients are (b) (4)

(b) (4) to yield the final tablets. The tablets are packaged in (b) (4) blister in (b) (4) a 10 count patient package.

NOCDURNA 25 mcg: White, round, orally disintegrating tablet with "25" on one side.
NDC 55566-5050-01 3 x 10 Unit Dose Blister Box of 30

(b) (4)

(b) (4)

The quality of the Nocdurna drug product is assured by visual inspection of the tablets, HPLC purity and impurity analysis, disintegration time, uniformity of mass and microbiological quality.

Chemistry Review

Real-time, long-term stability data have been provided in the NDA which indicate that the drug product is stable for up to 18 months. Data have been provided which demonstrate that the Nocdurna drug product is sensitive to light. Based on these data, the following expiry period is granted:

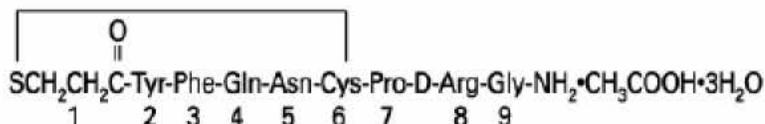
24 months when stored at 25 +/- 2°C/60 +/- 5% RH. Store protected from light.

The storage statement to be included in the PI is noted as follows:

“(b) (4) excursions permitted to 15 – 30°C (50 – 86°F). Keep in original package to protect from moisture and light. Use immediately upon opening individual tablet blister.”

Drug Substance

Desmopressin is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprise a desamination of the N-terminal and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin belongs to the pharmacologic class of posterior pituitary hormone. The molecular weight of desmopressin (as the acetate) is 1183.84 g/mole and the molecular formula is $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. The structure is indicated below:



Desmopressin acetate bulk drug substance is produced as a lyophilized powder and is consequently amorphous, i.e. there are no polymorphic forms. The synthesis and purification of this peptide is covered under DMF 8396. This DMF has been reviewed and is current; there are no outstanding CMC issues.

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

Nocdurna works by acting on in the collecting duct of the kidneys by increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency.

The proposed indication is for treatment of nocturia in adults. The tablets are intended to be placed under the tongue where they rapidly disintegrate (time < (b) (4)).

C. Basis for Approvability or Not-Approval Recommendation

This application is currently not recommended for approval from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. The following outstanding CMC review issues remain to be adequately addressed:

- An acceptable pre-approval inspection by the office of Compliance,
- Revised labeling for proposed containers and blisters for all intended dosage strengths.

Chemistry Review

III. Administrative**A. Reviewer's Signature**

See electronic signature block.

B. Endorsement Block

Same as electronic signature block.

C. CC Block

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

JOHN C HILL
03/09/2010

PRASAD PERI
03/09/2010
I concur

Product Quality Microbiology Review

12 February 2010

NDA: 22-517/N-000

Drug Product Name

Proprietary: Nocdurna

Non-proprietary: Desmopressin

Review Number: 1.

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
19 JUN 2009	22 JUN 2009	25 AUG 2009	27 AUG 2009
3 NOV 2009	3 NOV 2009	N/A	N/A

Applicant/Sponsor

Name: Ferring Pharmaceuticals, Inc.

Address: 4 Gatehall Dr.

Third Floor

Parsippany, NJ 07054

Representative: John Kim

Telephone: 973-796-1730

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
 2. **SUBMISSION PROVIDES FOR:** A new drug product.
 3. **MANUFACTURING SITE:**
Catalent UK Swindon Zydis Limited
Frankland Rd.
Blagrove, Swindon
Wiltshire, SN5 8RU
United Kingdom
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Orally Disintegrating Tablets.
 - Oral Ingestion.
 - 25 µg and 100 µg.
 5. **METHOD(S) OF STERILIZATION:** The subject drug product is not sterile.
 6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated for the treatment of nocturia in adults.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:**

The NDA is submitted electronically in the eCTD format.

A Microbiology Comment and Information Request were forwarded to the OND Project Manager for dissemination to the applicant on 02 October 2009.

Following is the IR:

Comment

It is understood that the release specification for the subject drug product includes a test method and acceptance criterion for (b) (4).

(b) (4)

Request for Information

Provide the following or reference to its location in the subject NDA:

- (b) (4)
- Data demonstrating that the microbial limits test methods are suitable for use with the subject drug product. Reference is

made to USP<61> which states in part, “The ability of the test to detect microorganisms in the presence of product to be tested must be established”.

The applicant amended the NDA with a response to this Request for Information on 03 November 2009. The responses are summarized and reviewed in appropriate sections of this review

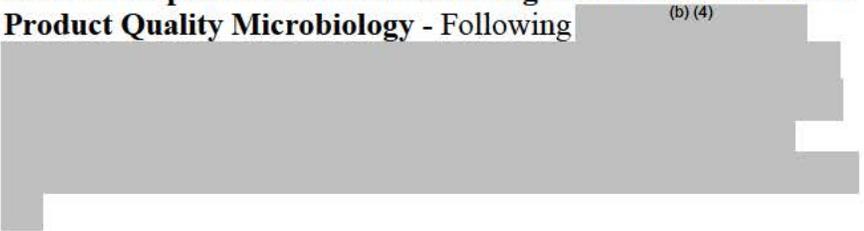
File Name: N022517R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 22-517/N-000 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - Following (b) (4)

- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. **Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** _____
Stephen Langille, Ph.D.
- C. **CC Block**
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance is desmopressin acetate. No further information regarding the subject drug substance is provided in the NDA.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product**

The subject drug product is an orally disintegrating tablet.

- **Drug product composition**

The composition of the 25 µg and 100 µg formulations of the subject drug product are presented in Tables 1 and 2, respectively.

Table 1. Composition of 25 µg formulation.

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.025 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 25 µg desmopressin free base.

Table 2. Composition of 100 µg formulation.

Component	Amount per unit	Function	Quality standard
Desmopressin*	0.100 mg	Drug Substance	Ph.Eur./USP, Curr. Ed.
Gelatin	(b) (4)		Ph.Eur./USP/JP, Curr. Ed.
Mannitol			Ph.Eur./USP, Curr. Ed.
Citric acid, anhydrous			Ph.Eur./USP, Curr. Ed.

*Each unit contains desmopressin acetate equivalent to 100 µg desmopressin free base.

- **Description of container closure system**

The container closure system consists of a blister with a (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity**

Container closure studies which demonstrate a microbial barrier are not needed for a non-sterile drug product.

- **Preservative Effectiveness**

The subject drug product is not preserved.

- Justification for not having a microbial limit specification for a non-sterile drug product**
 The drug product specification does include testing methods and acceptance criteria for microbial limits. Reference is made to Section P.5.1 of this review.

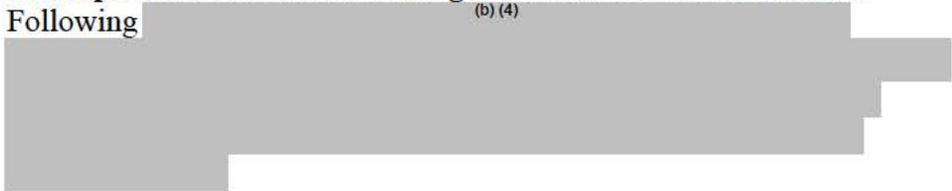
P.3 Manufacture

P.3.1 Manufacturer

Catalent UK Swindon Zydis Limited
 Frankland Rd.
 Blagrove, Swindon
 Wiltshire, SN5 8RU
 United Kingdom

P.3.3 Description of the Manufacturing Process and Process Controls

Following (b) (4)



P.5 Control of Drug Product

P.5.1 Specification

The product specification includes the test methods and acceptance criteria shown in Table 3 which are indicators of the microbiological quality of the subject drug product.

Table 3. Microbiological Tests and Acceptance Criteria *

Test	Method	Release and Stability Acceptance Criteria
Total Aerobic Microbial Count	Plate Count, Current USP	(b) (4)
Total Yeasts and Molds Count	Plate Count, Current USP	
Absence of <i>E. coli</i>	Plate Count, Current USP	

*Periodic release test (one batch of each strength/year) and routine stability test.

P.5.2 Analytical Procedures

• **Microbial Limits**

The applicant performs determination of Total Aerobic Microbial Count and Total Yeasts and Molds Count as per internal document AM713. The plate count method is performed according to USP. Accordingly, the applicant carried out verification studies to

demonstrate that the stated microbial limits testing methods are suitable for use with the subject drug product. These studies were documented in Summary Reports PR 182111 and PR 182113. The following challenge microbes were used in the studies:

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Bacillus subtilis*
- *Escherichia coli*
- *Candida albicans*
- *Aspergillus niger*

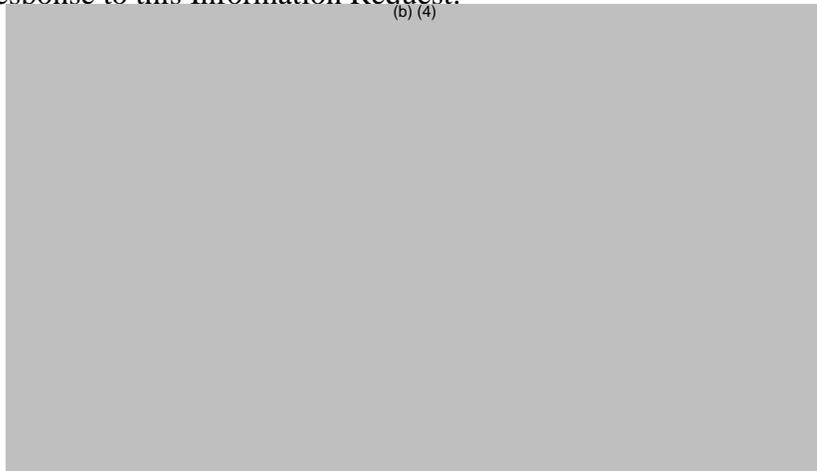
Reviewer's Comment

Review of the data presented in each of the Summary Reports reveals that the test methods for microbial limits are suitable for use with the subject drug product.

With regard to the frequency of the performance of this testing, the application states, "Periodic release test (one batch of each strength/year) and routine stability testing" (Table 3.2.P.5.1, Specification). The applicant presents the following rationale for performance of the microbial limits testing on a skip lot basis (Module 3.2.P.5.6):

"Since the results for microbiological quality of release batches are all well below the acceptance criteria, the tests will be performed periodically, one batch per strength per year".

In evaluating the applicant's plans for microbial limit skip lot testing, this reviewer requested additional information from the applicant regarding the (b) (4) (reference to the Information Request on Pages 2-3 of this review). The following information is summarized from the applicant's 03 November 2009 response to this Information Request:



(b) (4)

- Stability testing of the subject drug product has resulted in microbial limits data well below the established acceptance criteria. These data are compiled from stability studies supporting both the proposed drug product in the subject NDA, as well as the commercial production of the drug product for the European market (commercial production since 2005).

Satisfactory

Reviewer's Comments

- A. The microbial limits testing acceptance criteria are consistent with what is suggested in USP<1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* regarding nonaqueous preparations for oral use.
- B. The applicant's choice to perform microbial limits testing on a skip lot basis is acceptable for the following reasons:
 - Although the applicant did not present drug product A_w data, the information in Figure 1 (above) is useful for predicting A_w of the drug product at room temperature. It is generally accepted that below a A_w of 0.6, microbial growth is unlikely (1).
 - The applicant has presented microbial limits testing data from a total of 9 primary stability batches of the subject drug product (3 batches each of the 25 μg , 50 μg and 100 μg). In addition, microbial limits testing was performed on 8 supportive batches of product (30 μg , 60 μg and 120 μg). Microbial limits testing of all of these batches meet the microbial limits acceptance criteria.

Reference(b) (4)
**P.7 Container Closure System**

Reference is made to Section P.1 of this review.

P.8 Stability**P.8.1 Stability Summary and Conclusion**

The applicant has manufactured primary stability batches of the subject drug product at each of the three concentrations and monitored stability attributes for 18 months at long term conditions ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$), and 6 months at accelerated conditions ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$). The microbial limits tests are performed on the long term storage samples at initial time, 12 months, 24 months and 36 months.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to the placement of the first three batches of each strength of the subject drug product into the stability program.

P.8.3 Stability Data

Data from the stability testing of 9 primary stability batches and 8 supportive batches are provided in tables in Module 3.2.P.8.3 of the subject submission. The data derived from microbial limits testing meet the acceptance criteria provided in Table 3 of this review.

Satisfactory

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

Reference is made to Section A.2.1 of this review.

A.2.1 Materials of Biological Origin

The formulation of the drug product contains gelatin. The gelatin is manufactured from (b) (4) (Module 3.2.A.2). The subject submission contains a statement from the gelatin manufacturer ((b) (4)) certifying that the fish processing plants do not process ruminant material or other materials of TSE concern (deer, elk, sheep, goats, mink or cats).

Reviewer's Comment

This reviewer is not aware of any TSE risk to humans following the ingestion of raw materials derived from fish.

A.2.2 Testing at Appropriate Stages of Production

Not Applicable.

A.2.3 Viral Testing of Unprocessed Bulk

Not Applicable.

A.2.4 Viral Clearance Studies

The subject submission does not include data from viral inactivation studies. However, it is stated that the gelatin manufacturing process “contains several steps where a virus would be eliminated in the unlikely event that it could be present in our raw materials” ((b) (4) Fish Gelatin –Statement on Viral Safety; Module 3.2.A.2). Examples include:

- (b) (4)
- (b) (4)
- (b) (4)

Reviewer's Comment

The (b) (4) steps would inactivate/remove viruses.

R REGIONAL INFORMATION**R.1 Executed Batch Record**

The subject submission includes copies of the batch record.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**A. PACKAGE INSERT**

This reviewer has no comment regarding the package insert.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: There are no microbiology deficiencies identified.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN W METCALFE
02/12/2010

STEPHEN E LANGILLE
02/12/2010



NDA 22-517

Nocdurna (desmopressin) Orally Disintegrating Tablet

Ferring Pharmaceuticals Inc.

John C. Hill, Ph.D.

ONDQA/DPMA-1 and OND/ODE II/DMEP

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Chemistry Review Data Sheet

1. NDA 22-517
2. REVIEW #:1
3. REVIEW DATE: 28-SEP-2009
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 65,890

Document Date

FE992026 (desmopressin melt)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed22-517 (Original NDA Application)
(Responses to CMC filing deficiencies)Document Date22-JUN-2009
24-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals
Address:	4 Gatehall Drive Third Floor Parsippany, NJ 07054
Representative:	Ronald T. Hargreaves, Ph.D., Director Regulatory Affairs
Telephone:	973-769-1730

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nocdurna

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Desmopressin acetate
c) Code Name/# (ONDC only): Desmopressin Melt
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

LISTED REFERENCE: Sanofi-Adentis, DDAVP (desmopressin acetate) tablets

10. PHARMACOL. CATEGORY: Treatment of nocturina in adults

11. DOSAGE FORM: Orally Disintegrating Tablet (OTD)

12. STRENGTH/POTENCY: 25 and 100 mg strengths

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

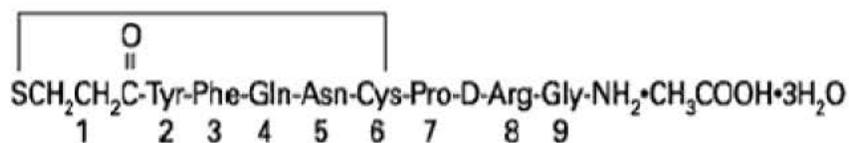
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Established Name: desmopressin acetate

IUPAC Name: 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetats (salt) trihydrate.

Structural Formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
8396	II	PolyPeptide Laboratories (sweeden) AB	Desmopressin	1	Adequate	18-AUG-2009	Update review of DMF

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,890	FE992026 (desmopressin melt)
NDA	19-955	DDAVP tablets
NDA	21-333	Minirin Nasal Spray
NDA	21-798	Desmopressin acetate tablets
DMF	8396	Poly-Peptides Laboratories AB: Desmopressin acetate drug substance

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	17-SEP-2009	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Pharm/Tox			
Biopharm	NA		
LNC			
Methods Validation	Pending	28-SEP-2009	
OPDRA			
EA	Adequate	28-SEP-2009	John Hill
Microbiology	Pending	28-SEP-2009	

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-517

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Control (CMC) point of view, this NDA is approvable pending adequate and satisfactory resolution of the following items:

- Adequate responses to the noted CMC deficiencies,
- An acceptable pre-approval inspection by the Office of Compliance,
- Revised labeling for proposed containers and blisters for all intended dosage strengths.

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

The applicant must agree to annually enroll one batch of each tablet strength into the long-term stability program.

II. Summary of Chemistry Assessments

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

Drug Product

Nocdurna is formulated as an orally disintegrating tablet and supplied in two dosage strengths: 25 and 100 mcg of desmopressin (as the free base). Nocdurna contains the active ingredient desmopressin (as the free base) and the following excipients: gelatin (derived from fish), mannitol and citric acid. These ingredients are (b) (4)

(b) (4) to yield the final tablets. The tablets are packaged in an (b) (4) blister in (b) (4) a 10 count patient package. The quality of the Nocdurna drug product is assured by visual inspection of the tablets, HPLC purity and impurity analysis, disintegration time, uniformity of mass and microbiological quality.

Real-time, long-term stability data have been provided in the NDA which indicate that the drug product is stable for up to 18 months. Data have been provided which demonstrate that the Nocdurna drug product is sensitive to light. Based on these data, the following expiry period is granted:

24 months when stored at 25 +/- 2°C/60 +/- 5% RH. Store protected from light.

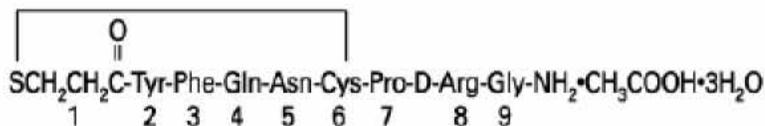
Additional information will be requested in order to evaluate the proposed/requested expiry dating of 36 months.

Drug Substance

Desmopressin is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone. The modifications comprise a desamination of the N-terminal

Executive Summary Section

and a replacement of L-arginine by D-arginine in position 8 in the peptide sequence. Desmopressin belongs to the pharmacologic class of posterior pituitary hormone. The molecular weight of desmopressin (as the acetate) is 1183.84 g/mole and the molecular formula is $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. The structure is indicated below:



Desmopressin acetate bulk drug substance is produced as a lyophilized powder and is consequently amorphous, i.e. there are no polymorphic forms. The synthesis and purification of this peptide is covered under DMF 8396. This DMF has been reviewed and is current; there are no outstanding CMC issues.

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

Nocturna works by acting on in the collecting duct of the kidneys by increasing urine concentration and decrease urine production, which in turns leads to decrease in voiding frequency.

The proposed indication is for treatment of nocturia in adults. The tablets are intended to be placed under the tongue where they rapidly disintegrate (time < (b) (4)).

C. Basis for Approvability or Not-Approval Recommendation

This application is currently not recommended for approval from a CMC viewpoint. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(2) application. The following outstanding CMC review issues remain to be adequately addressed:

- Adequate responses to the noted CMC deficiencies,
- An acceptable pre-approval inspection by the office of Compliance,
- Revised labeling for proposed containers and blisters for all intended dosage strengths.

III. Administrative

A. Reviewer's Signature

See electronic signature block.

B. Endorsement Block

Same as electronic signature block.

C. CC Block

51 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

JOHN C HILL
10/19/2009

PRASAD PERI
10/21/2009