CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-795

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21795/000	Action Goal:	
Stamp:	04-MAR-2005	District Goal:	05-NOV-2005
Regulatory Due:	27-MAR-2008	Brand Name:	MINIRIN (DESMOPRESSIN
Applicant:	FERRING PHARMS	Estab. Name:	ACETATE) 0.1/0.2MG
	4 GATEHALL DR 3RD FL	Generic Name:	DESMOPRESSION ACETATE
	PARSIPPANY, NJ 07054		TABLETS
Priority:	5S	Dosage Form:	(TABLET)
Org Code:	510	Strength:	0.1 MG AND 0.2 MG

Application Comment: APPLICATION RESUBMITTED/COMPLETE RESPONSE SUBMITTED 24 SEP 2007. REVIEWER INDICATES THAT PREVIOUS EES EVALUATION WILL EXPIRE DURING REVIEW CYCLE. REVIEWER NOTES NO CHANGES TO ESTABLISHMENT LIST. (on 26-OCT-2007 by S. GOLDIE () 301-796-2055)

FDA Contacts:	L. ALJUBURI	301-796-1168 , Project Manager
	J. HILL	301-796-1679 , Review Chemist
	S. MOORE	301-796-1718 , Team Leader

Overall Recommendation: ACCEPTABLE on 26-MAR-2008by S. ADAMS (HFD-325)301-796-3193
ACCEPTABLE on 07-DEC-2005by S. ADAMS (HFD-325)301-796-3193

Establishment: CFN FEI

[redacted] b(4)

No: AADA:

Responsibilities: [redacted] b(4)

Profile: CSN OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR MANUFACTURE OF SYNTHETIC PEPTIDE (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	03-MAY-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	11-MAY-2005	GMP			ADAMSS
INSPECTION SCHEDULED	26-AUG-2005		15-SEP-2005		IRIVERA
INSPECTION PERFORMED	15-SEP-2005		15-SEP-2005		ADAMSS
DO RECOMMENDATION	07-DEC-2005			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	07-DEC-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-OCT-2007				GOLDIES
SUBMITTED TO DO	26-OCT-2007	GMP			ADAMSS
DO RECOMMENDATION	20-NOV-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMS
OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN [redacted] FEI [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: [redacted] (on

03-MAY-2005 by J. HILL () 301-796-1679) b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	04-MAY-2005	GMP			ADAMSS
DO RECOMMENDATION	19-MAY-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	19-MAY-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-OCT-2007				GOLDIES
SUBMITTED TO DO	26-OCT-2007	GMP			ADAMSS
ASSIGNED INSPECTION T	20-NOV-2007	GMP			ADAMSS
INSPECTION SCHEDULED	21-MAR-2008		08-APR-2008		IRIVERA
DO RECOMMENDATION	26-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS

PER ACTG TEAM LEADER. S. LASKA. AFTER REVIEW OF PREVIOUS INSPECTION AND OTHER GMP INFORMATION PROVIDED BY FERRING. THIS SITE WAS INSPECTED IN 5/04 AND CLASSIFIED VAI FOR DRUG PRODUCT METERED DOSE INHALER FOR DESMOPRESSIN ACETATE AND SUBSEQUENTLY INSPECTED BY

[redacted] IN NOVEMBER 2006. TWO LICENSES WERE ISSUED BY [redacted] THE PENDING APPLICATION IS FOR DESMOPRESSIN ACETATE TABLETS. b(4)

RECOMMEND PROCEED WITH SITE CONCURRENCE AND ANY COMPLIANCE MATTERS WILL BE COVERED ON A POST APPROVAL BASIS DURING THE PLANNED EI OF 4/08.

OC RECOMMENDATION 26-MAR-2008 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

SEE DO RECOMMENDATION COMMENTS.

Establishment: CFN FEI [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment: CONTRACT LABORATORY FOR MICROBIOLOGICAL TESTING (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	04-MAY-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	06-MAY-2005	GMP			ADAMSS
INSPECTION SCHEDULED	05-AUG-2005		20-SEP-2005		ADAMSS
INSPECTION PERFORMED	20-SEP-2005		20-SEP-2005		ADAMSS
DO RECOMMENDATION	07-DEC-2005			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	07-DEC-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
MITTED TO OC	26-OCT-2007				GOLDIES
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ASSIGNED INSPECTION T	20-NOV-2007	GMP			ADAMSS
INSPECTION SCHEDULED	21-MAR-2008		11-APR-2008		IRIVERA
DO RECOMMENDATION	24-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
POST APPROVAL INSPECTION TO OCCUR					
OC RECOMMENDATION	24-MAR-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN FEI

b(4)

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DISTRICT RECOMMENDATION

APPEARS THIS WAY ON ORIGINAL

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR CHEMICAL TESTING ON RAW MATERIAL (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	04-MAY-2005	GMP			ADAMSS
DO RECOMMENDATION	06-MAY-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
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ASSIGNED INSPECTION T	20-NOV-2007	GMP			ADAMSS
DO RECOMMENDATION	24-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAM
POST APPROVAL INSPECTION TO OCCUR					
OC RECOMMENDATION	24-MAR-2008			ACCEPTABLE	ADAMSS

APPEARS THIS WAY ON ORIGINAL

3/26/08

MEMORANDUM

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

DATE: 26-MAR-2008

TO: Jennifer Johnson Project Manager (HFD-510)
File, NDA 21-795

THROUGH: Ali Al-Hakim, Ph.D., Chief, Branch II, DMA-I

FROM: John Hill, Ph.D., Chemistry Reviewer Branch II, DMA-I

SUBJECT: **NDA 21-795: Establishment Inspection Results And Recommendation on Approvability**

Establishment Evaluation

The Office of Compliance (OC) has finished their evaluation of manufacturing facilities in support of NDA application 21-795. A copy of the OC report is attached to this memo. Per Establishment Evaluation Summary Report dated 26-MAR-2008, the overall recommendation form the Office of Compliance is **acceptable**.

Recommendation and Conclusion on Approvability of NDA 21-795

NDA 21-795 is recommended for approval from the standpoint of chemistry, manufacturing and controls.

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21795/000	Action Goal:	
Stamp:	04-MAR-2005	District Goal:	05-NOV-2005
Regulatory Due:	27-MAR-2008	Brand Name:	MINIRIN (DESMOPRESSIN
Applicant:	FERRING PHARMS	Estab. Name:	ACETATE) 0.1/0.2MG
	4 GATEHALL DR 3RD FL	Generic Name:	DESMOPRESSION ACETATE
	PARSIPPANY, NJ 07054		TABLETS
Priority:	5S	Dosage Form:	(TABLET)
Org Code:	510	Strength:	0.1 MG AND 0.2 MG

Application Comment: APPLICATION RESUBMITTED/COMPLETE RESPONSE SUBMITTED 24 SEP 2007. REVIEWER INDICATES THAT PREVIOUS EES EVALUATION WILL EXPIRE DURING REVIEW CYCLE. REVIEWER NOTES NO CHANGES TO ESTABLISHMENT LIST. (on 26-OCT-2007 by S. GOLDIE () 301-796-2055)

FDA Contacts:	L. ALJUBURI	301-796-1168	, Project Manager
	J. HILL	301-796-1679	, Review Chemist
	S. MOORE	301-796-1718	, Team Leader

Overall Recommendation: ACCEPTABLE on 07-DEC-2005by S. ADAMS (HFD-325)301-796-3193

Establishment: CFN FEI

b(4)

[redacted]

[redacted] No: AADA:

[redacted] onsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR MANUFACTURE OF SYNTHETIC PEPTIDE (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	03-MAY-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	11-MAY-2005	GMP			ADAMSS
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APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN [redacted] FEI [redacted]

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: RESPONSIBLE FOR MANUFACTURING, PACKAGING, QC TESTING, AND RELEASE (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-MAY-2005				HILLJ
SUBMITTED TO DO	04-MAY-2005	GMP			ADAMSS
DO RECOMMENDATION	19-MAY-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
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ASSIGNED INSPECTION T	20-NOV-2007	GMP			ADAMSS
INSPECTION SCHEDULED	21-MAR-2008		08-APR-2008		IRIVERA

Establishment: CFN FEI [redacted]

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR MICROBIOLOGICAL TESTING (on 03-MAY-2005 by J. HILL () 301-796-1679)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
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APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

INSPECTION SCHEDULED	21-MAR-2008	11-APR-2008		IRIVERA
DO RECOMMENDATION	24-MAR-2008		ACCEPTABLE	ADAMSS
			BASED ON FILE REVIEW	
POST APPROVAL INSPECTION TO OCCUR				
OC RECOMMENDATION	24-MAR-2008		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

Establishment: CFN FEI

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR CHEMICAL TESTING ON RAW MATERIAL (on 03-MAY-2005 by J. HILL () 301-796-1679)

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APPEARS THIS WAY ON ORIGINAL

Profile: CSN OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR MANUFACTURE OF SYNTHETIC PEPTIDE (on 03-MAY-2005 by J. HILL () 301-796-1679)

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OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

APPEARS THIS WAY ON ORIGINAL

DRUG PRODUCT METERED DOSE INHALER FOR DESMOPRESSIN ACETATE AND SUBSEQUENTLY INSPECTED BY [redacted] IN NOVEMBER 2006. TWO LICENSES WERE ISSUED BY [redacted] THE PENDING APPLICATION IS FOR DESMOPRESSIN ACETATE TABLETS. b(4)

RECOMMEND PROCEED WITH SITE CONCURRENCE AND ANY COMPLIANCE MATTERS WILL BE COVERED ON A POST APPROVAL BASIS DURING THE PLANNED EI OF 4/08.

OC RECOMMENDATION 26-MAR-2008 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

SEE DO RECOMMENDATION COMMENTS.

Establishment: CFN FEI [redacted] b(4)

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

APPEARS THIS WAY ON ORIGINAL

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: CONTRACT LABORATORY FOR CHEMICAL TESTING ON RAW MATERIAL (on 03-MAY-2005 by J. HILL () 301-796-1679)

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				BASED ON FILE REVIEW	
POST APPROVAL INSPECTION TO OCCUR					
OC RECOMMENDATION	24-MAR-2008			ACCEPTABLE	ADAMSS

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

/s/

John C. Hill
3/26/2008 02:36:43 PM
CHEMIST

Ali Al-Hakim
3/26/2008 02:38:48 PM
CHEMIST

MINIRIN (desmopressin acetate) tablets
NDA 21-795

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

Applicant: Ferring Pharmaceuticals
400 Rella Boulevard, Suite 300
Suffern New York 10901

Indication: Treatment of Central diabetes insipidus, Primary nocturnal enuresis, Renal concentration capacity test.

Presentation: Tablet containing 0.1 mg or 0.2 mg desmopressin acetate formulated with lactose, potato starch, magnesium stearate and povidone. The tablets are packaged in a 30 ml [redacted] container/closure system with an [redacted] desiccant at either 7 count or 100 count per bottle. b(4)

EER Status: Acceptable 07-DEC-2005

Consults: DMETS – Tradename- Acceptable 08-DEC-2005
DSI-Audit of Clinical Study Sites- Not acceptable 05-DEC-2005
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested

Original Submission: 02-MAR-2005

Post-Approval Agreements:

The applicant agrees to place one batch of each strength, in the approved container/closure, annually, in the post-approval stability program, if any batches are manufactured.

Drug Substance

Desmopressin acetate, a synthetic peptide analogue of the natural pituitary hormone, 8-arginine vasopressin (ADH), is an antidiuretic hormone affecting renal water conservation. Desmopressin acetate is composed of 9 amino acids. The purification process includes several [redacted] steps prior to desmopressin being formulated into bulk drug substance. This bulk drug substance is produced as a [redacted] b(4)

The synthesis, purification, characterization and stability of this peptide is covered under DMF [redacted] This DMF has been reviewed and is current; there are no outstanding CMC issues. b(4)

Conclusion: Drug substance is acceptable.

Drug Product

Minirin tablets contain either 0.1 or 0.2 mg desmopressin acetate. Inactive ingredients used in the formulation of the Minirin tablets include: lactose, potato starch, magnesium stearate and povidone. In the commercial drug product manufacturing process, desmopressin acetate and the excipients are combined [redacted] b(4)

Specifications for the drug product include: visual description, identification by HPLC, assay by HPLC, purity, impurity and content uniformity by HPLC, residual water content, disintegration, dissolution and microbial testing. All tests methods have been appropriately validated for their intended purpose. The dissolution data provided demonstrate that the subject drug and the listed drug are comparable.

Stability data for the drug product have been provided for up to 12 months at 25°C/65% Relative Humidity (RH) and 6 months at 40°C/75%RH. All available stability results are within the proposed specifications; no significant changes in drug product quality attributes have been detected. Based on the provided real-time stability data and supporting developmental stability data the proposed expiry period of 24 months is acceptable. The label claim for storage and expiry will be "Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [See USP]. Avoid exposure to excessive heat or light".

Conclusion: Drug product is satisfactory.

Additional Items:

Validation package, describing the test methods and validation procedures, including information supporting the reference standard, is adequately provided. As the analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry, revalidation by Agency laboratories will not be requested

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

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

APPEARS THIS WAY ON ORIGINAL

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

/s/

Blair Fraser
12/16/2005 10:53:58 AM
CHEMIST

NDA 21-795

MINIRIN (desmopressin acetate) tablets

Ferring Pharmaceuticals

John C. Hill, Ph.D., Chemistry Reviewer
ONDC / DPMAI / DMEP / HFD-510

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-795

2. REVIEW # 2

3. REVIEW DATE: 14-DEC-2005

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	17-NOV-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Filing	02-MAR-2005
BL Amendment	27-APR-2005
BZ Amendment	27-SEP-2005
BC Amendment	06-DEC-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals
Address:	400 Rella Boulevard, Suite 300 Suffern New York 10901
Representative:	Ronald T. Hargreaves, Ph.D., Executive Director Regulatory Affairs
Telephone:	845-770-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MINIRIN Tablets

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

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)
Listed Drugs: DDAVP Tablets, Aventis
CONCENTRAID Intranasal Solution, Ferring

10. PHARMACOL. CATEGORY: Central diabetes insipidus Primary nocturnal enuresis, Renal concentration capacity test.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.1 mg and 0.2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

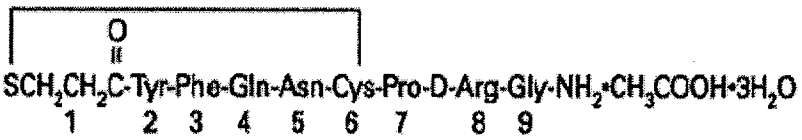
___X___Not a SPOTS product

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

Established Name: desmopressin acetate

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

Structural Formula:



molecular Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \bullet C_2H_4O_2 \bullet 3H_2O$

Molecular Weight: 1183.34

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Desmopressin acetate drug substance	4	Adequate	24-FEB-2003	LOA 11-JAN-2005 (Vol 4, p 268)
[redacted]	III	[redacted]	[redacted]	4	Adequate	13-JAN-1998	LOA 25-JAN-2005 (Vol 4, p 270)

b(4)

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	07-DEC-2005	S. Adams
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	30-AUG-2005	John Hill, Ph.D.
Microbiology			

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 21-795

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From A CMC viewpoint, this application can be approved. An expiry period of 24 months for the drug product is granted as requested. See labeling comment to be communicated to the applicant.

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

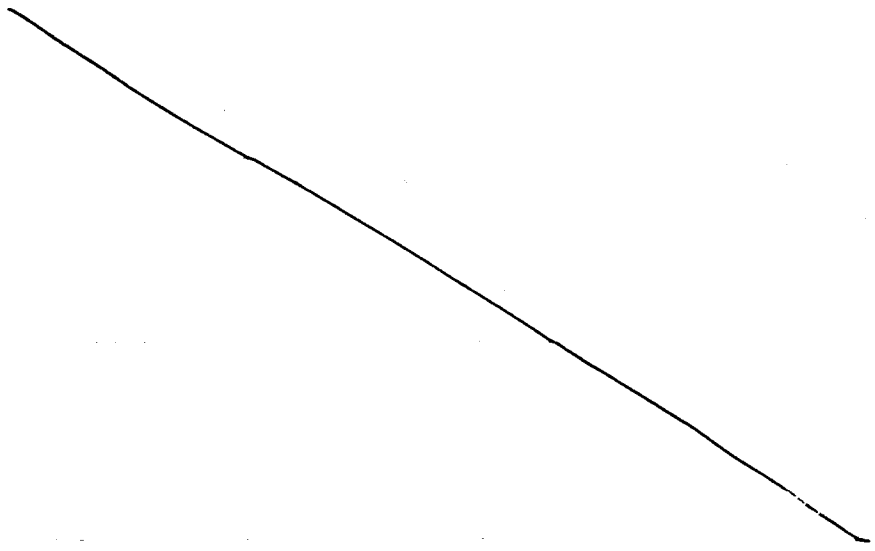
The applicant agrees to place one batch of each strength, in the approved container/closure, annually in the post-approval stability program, if any batches are manufactured.

II. Summary of Chemistry Assessments

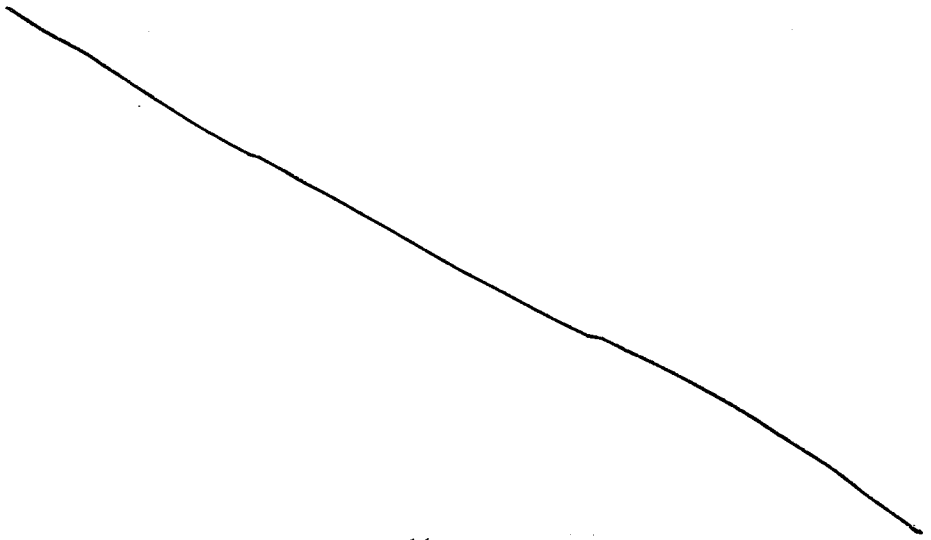
A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

Minirin tablets contain either 0.1 or 0.2 mg desmopressin acetate. Inactive ingredients used in the formulation of the Minirin tablets include: lactose, potato starch, magnesium stearate and povidone.



b(4)



b(4)

The tablets are packaged in a 30 ml [redacted] container/closure system with an [redacted] desiccant at either 7 count or 100 count per bottle. The current batch size, for both tablet strengths, is [redacted] which equals [redacted] tablets, with a target weight of 200 mg/tablet.

b(4)

Specifications for the drug product include: visual description, identification by HPLC, assay by HPLC, purity, impurity and content uniformity by HPLC, residual water content, disintegration, dissolution and microbial testing. All tests methods have been appropriately validated for their intended purpose. The dissolution data provided demonstrate that the subject drug and the listed drug are comparable.

Stability data for the drug product have been provided for up to 12 months at 25°C/65% Relative Humidity (RH) and 6 months at 40°C/75%RH. All available stability results are within the proposed specifications; no significant changes in drug product quality attributes have been detected. Factors influencing tablet stability (measured as content of drug substance and sum of impurities) were identified as the amount of [redacted] present in the [redacted] and high humidity in the drug product. These studies demonstrated that degradation products form much faster under humid conditions (40°C/75%RH) than under dry conditions (25°C/60%RH and 40°C/ambient). These stability concerns were addressed by tightening the acceptable limit for [redacted] in the [redacted] and assuring [redacted] and a suitable packaging material for the drug product. Based on the provided real-time stability data and supporting developmental stability data the proposed expiry period of 24 months is acceptable. The label claim for storage and expiry will be "Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [See USP]. Avoid exposure to excessive heat or light".

b(4)

b(4)

2. Drug Substance

Desmopressin acetate, a synthetic peptide analogue of the natural pituitary hormone, 8-arginine vasopressin (ADH), is an antidiuretic hormone affecting renal water conservation. Desmopressin acetate is composed of 9 amino acids. The purification process includes several [redacted] steps prior to desmopressin being formulated into bulk drug substance. This bulk drug substance is produced as a [redacted]. The synthesis and purification of this peptide is covered under DMF [redacted] This DMF has been reviewed and is current; there are no outstanding CMC issues. b(4) b(4)

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

1.) Central Diabetes Insipidus

Minirin tablets are proposed to be indicated as antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. The optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses.

2.) Primary Nocturnal Enuresis

Minirin tablets are also proposed to be indicated for the management of primary nocturnal enuresis in children and adults [redacted] Minirin may be used alone or as an adjunct to behavioral conditioning or other nonpharmacologic intervention. The dose may be titrated up to 0.6 mg at bedtime to achieve the desired response. b(4)

3.) Renal Concentration Capacity Test

Minirin tablets are also proposed to be used to determine the capacity of the kidney to concentrate urine. Minirin tablets 0.6 mg (3 x 0.2 mg) should be taken at bedtime after bladder emptying.

C. Basis for Approvability or Not-Approval Recommendation

This application can be approved 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. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. The deficiencies communicated to the sponsor have been adequately addressed.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist: Same date as electronic review
Stephen K. Moore, Ph.D., Team Leader/Pharmaceutical Assessment Lead: Same date as electronic review
Blair A. Fraser, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Lina Aljuburi, PharmD., MS., Regulatory Project Manager

APPEARS THIS WAY ON ORIGINAL

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

John C. Hill
12/16/2005 10:41:37 AM
CHEMIST

Blair Fraser
12/16/2005 10:44:32 AM
CHEMIST

NDA 21-795

MINIRIN (desmopressin acetate) tablets

Ferring Pharmaceuticals

John C. Hill, Ph.D., Chemistry Reviewer
ONDC / DPMAI / DMEP / HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-795

2. REVIEW # 1

3. REVIEW DATE: 30-AUG-2005

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Filing	02-MAR-2005
BL Amendment	27-APR-2005
BZ Amendment	27-SEP-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals
Address:	400 Rella Boulevard, Suite 300 Suffern New York 10901
Representative:	Ronald T. Hargreaves, Ph.D., Executive Director Regulatory Affairs
Telephone:	845-770-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MINIRIN Tablets
b) Non-Proprietary Name (USAN): Desmopressin acetate tablets

c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)
Listed Drugs: DDAVP Tablets, Aventis
CONCENTRAID Intranasal Solution, Ferring

10. PHARMACOL. CATEGORY: Central diabetes insipidus Primary nocturnal enuresis, Renal concentration capacity test.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.1 mg and 0.2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

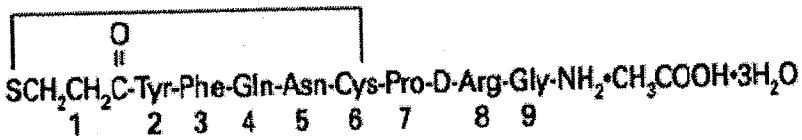
___X___Not a SPOTS product

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

Established Name: desmopressin acetate

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

Structural Formula:



molecular Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

Molecular Weight: 1183.34

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Desmopressin acetate drug substance	4	Adequate	24-FEB-2003	LOA 11-JAN-2005 (Vol 4, p 268)
[redacted]	III	[redacted]	[redacted]	[redacted]	Adequate	13-JAN-1998	LOA 25-JAN-2005 (Vol 4, p 270)

b(4)

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	30-AUG-2005	John Hill, Ph.D.
Microbiology			

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 21-795

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From A CMC viewpoint, this application is approvable (AE). The outstanding issues are:
1.) Acceptable CGMP status for pending pre-approval site inspections,
2.) Satisfactory resolution of CMC deficiencies.

Based on the provided real-time stability data and supporting developmental stability data the proposed expiry period of 24 months is granted.

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

There are no phase 4 (post-marketing) commitments.

II. Summary of Chemistry Assessments

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

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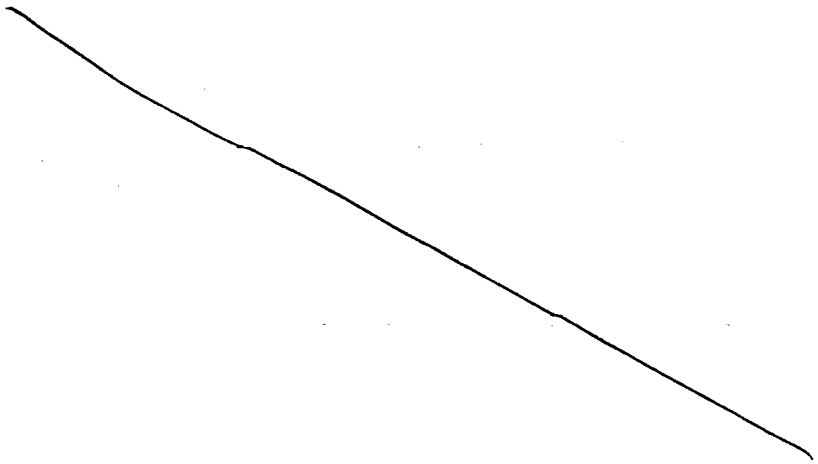

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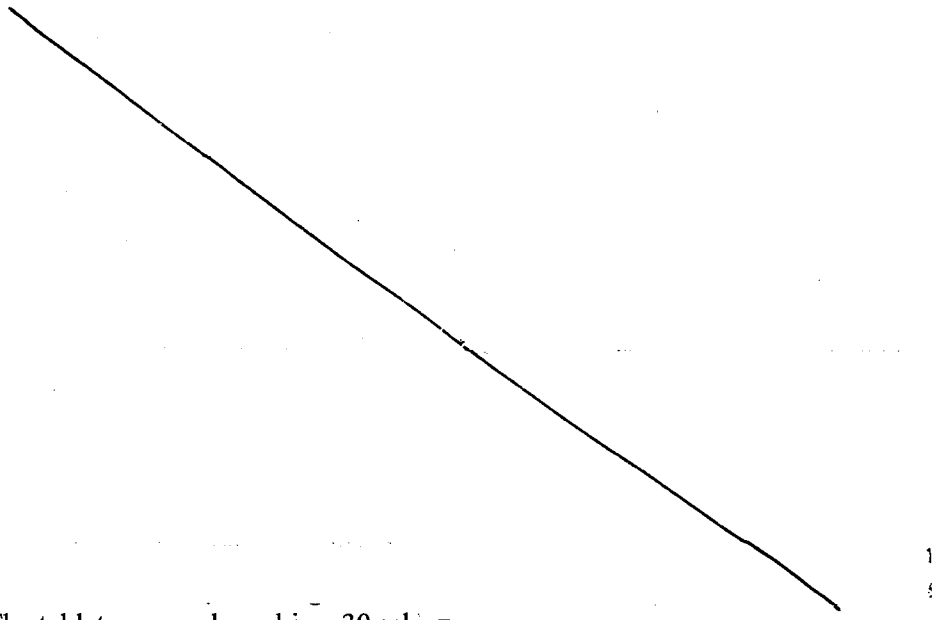

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C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) 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. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. However, certain CMC deficiencies remain be addressed. The CGMP facility inspections are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist: Same date as electronic review
Stephen K. Moore, Ph.D., Team Leader/Pharmaceutical Assessment Lead: Same date as electronic review
Blair A. Fraser, Ph.D., Branch Chief: Same date as electronic review

C. CC Block

Lina Aljuburi, PharmD., MS., Regulatory Project Manager

APPEARS THIS WAY ON ORIGINAL

39 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

John C. Hill
11/17/2005 07:19:39 AM
CHEMIST

Blair Fraser
11/17/2005 02:12:39 PM
CHEMIST

Stephen Moore
11/17/2005 04:33:31 PM
CHEMIST