

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-795

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21,795

NAME OF APPLICANT / NDA HOLDER
Ferring Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
MINIRIN

ACTIVE INGREDIENT(S)
Desmopressin Acetate

STRENGTH(S)
0.1 mg and 0.2 mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number US 7,022,340 B2	b. Issue Date of Patent 04/04/2006	c. Expiration Date of Patent 04/30/2023
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d. Name of Patent Owner Ferring B.V.	Address (of Patent Owner) Polaris Avenue 144	
	City/State Hoofddorp / Netherlands 2132 JX	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) <input checked="" type="checkbox"/> Ronald T. Hargreaves, Ph.D.	Address (of agent or representative named in 1.e.) Ferring Pharmaceuticals Inc. 400 Rella Blvd, Suite 300	
	City/State Suffern, New York	
	ZIP Code 10901	FAX Number (if available) (845) 770-2694
	Telephone Number (845) 770-2620	E-Mail Address (if available) Ron.Hargreaves@Ferring.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Ronald T. Hargreaves

4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Ronald T. Hargreaves, Ph.d.

Address

Ferring Pharmaceuticals
400 Rella Blvd, Suite 300

City/State

Suffern, New York

ZIP Code

10901

Telephone Number

(845) 770-2620

FAX Number (if available)

(845) 770-2694

E-Mail Address (if available)

Ron.Hargreaves@Ferring.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

New Drug Application 21- 795
MINIRIN (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg
Ferring Pharmaceuticals Inc., 4 Gatehall Drive, Third Floor, Parsippany, NJ 07054

Paragraph IV Certification:

The undersigned certifies that US Patent 7,022,340 will not be infringed by the manufacture, use or sale of MINIRIN Tablets, for which this application is submitted.

Ronald T. Hargreaves.

Ronald T. Hargreaves, Ph.D.
Vice President
Regulatory Affairs
Ferring Pharmaceuticals Inc.

3/17/08

Date

APPEARS THIS WAY ON ORIGINAL

New Drug Application 21- 795
MINIRIN (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg
Ferring Pharmaceuticals Inc., 400 Rella Blvd., Suffern, NY 10901

Patent Certification

Ferring Pharmaceuticals Inc. has been granted a license to U.S. Patents 5,500,413, 5,674,850 and 5,763,407 by the patents' owner, Ferring B.V. Ferring Pharmaceuticals Inc. and Ferring B.V. are affiliates of Ferring Holding S.A.

Ferring Pharmaceuticals Inc. will comply with the requirements of 21 CFR 314.52(a) and 21 CFR 314.52(c) by providing notice of the Paragraph IV Certification below to Ferring B.V. and to Aventis Pharmaceuticals, the holder of NDA 19-955 for DDAVP Tablets.

There are no other U.S. patents known to the applicant which claim the drug substance, composition/formulation or method of use for the drug covered by this application.

Paragraph IV Certification:

The undersigned certifies that US Patents 5,500,413, 5,674,850 and 5,763,407 will not be infringed by the manufacture, use or sale of MINRIN tablets, for which this application is submitted.

Ronald T. Hargreaves
Ronald T. Hargreaves, Ph.D.
Executive Director
Regulatory Affairs
Ferring Pharmaceuticals Inc.

4/12/05
Date

13. Patent Information

U.S. Patent Number: 5,047,398

Expiration Date: Sept. 10, 2008

Type of patent (indicate all that apply):

Drug substance (active ingredient)	<input type="checkbox"/> Y	<input checked="" type="checkbox"/> N
Drug product (composition/formulation)	<input checked="" type="checkbox"/> Y	<input type="checkbox"/> N
Method of use	<input checked="" type="checkbox"/> Y	<input type="checkbox"/> N

Name of patent owner:

Ferring B.V., Hoofddorp, The Netherlands

U.S. Agent (if patent owner or applicant does not reside or have a place of business in the U.S.)

Ferring Pharmaceuticals Inc.
400 Rella Blvd.
Suite 300
Suffern, NY 10901

The undersigned declares that the above United States Patent, number 5,047,398, covers the composition, formulation and/or method of use of MINIRIN Tablets. This product is:

currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

or

the subject of this application for which approval is being sought.

Signed:

Ronald T. Hargreaves
Ronald T. Hargreaves, Ph.D.

Title: Executive Director, regulatory Affairs

Date:

3/2/05

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT
For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER

21-795

NAME OF APPLICANT / NDA HOLDER

Ferring Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

MINIRIN Tablets

ACTIVE INGREDIENT(S)

Desmopressin acetate

STRENGTH(S)

0.1 mg , 0.2 mg

DOSAGE FORM

Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,047,398

b. Issue Date of Patent

09/10/1991

c. Expiration Date of Patent

09/10/2008

d. Name of Patent Owner

Ferring B.V.

Address (of Patent Owner)

City/State

Hoofddorp, The Netherlands

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

Ferring Pharmaceuticals Inc.

400 Rella Blvd., Suite 300

City/State

Suffern, NY

ZIP Code

10901

FAX Number (if available)

(845) 770-2663

Telephone Number

(845) 770-2620

E-Mail Address (if available)

ron.hargreaves@ferring.com

 Ronald T. Hargreaves, Ph.D.
Executive Director, Regulatory Affairs

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 6 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
 1. Central diabetes insipidus
 2. Primary nocturnal enuresis
 3. Renal concentrating capacity test

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Ronald T. Hargreaves

3/2/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Ronald T. Hargreaves, Ph.D.

Address

Ferring Pharmaceuticals Inc.
400 Rella Blvd.

City/State

Suffern, NY

ZIP Code

10901

Telephone Number

(845) 770-2620

FAX Number (if available)

(845) 770-2663

E-Mail Address (if available)

ron.hargreaves@ferring.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

14. Patent Certification

Ferring Pharmaceuticals Inc. has been granted a license to U.S. Patent 5,047,398, by the patent owner, Ferring B.V. Ferring Pharmaceuticals Inc. and Ferring B.V. are affiliates of Ferring Holding S.A.

Ferring Pharmaceuticals Inc. will comply with the requirements of 21 CFR 314.52(a) and 21 CFR 314.52(c) by providing notice of the Paragraph IV Certification below to Ferring B.V. and to Aventis Pharmaceuticals, the holder of NDA 19-955 for DDAVP Tablets.

There are no other U.S. patents known to the applicant which claim a composition/formulation or method of use for the drug covered by this application.

Paragraph IV Certification:

The undersigned certifies that US Patent 5,047,398 will not be infringed by the manufacture, use or sale of MINRIN tablets, for which this application is submitted.

Ronald T. Hargreaves
Ronald T. Hargreaves, Ph.D.
Executive Director
Regulatory Affairs

3/2/05
Date

EXCLUSIVITY SUMMARY

NDA # 21-795

SUPPL # N/A

HFD # 510

Trade Name Approved without trade name

Generic Name desmopressin acetate; Dosage Form = tablets

Applicant Name Ferring Pharmaceuticals, Inc.

Approval Date, If Known May 8, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

Note: the reference product is DDAVP (desmopressin acetate) Tablets, NDA 19-955.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

number of years not noted in application

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 45A06-53: Long term double-blind, randomized multicentre study to compare two doses of desmopressin tablets in the management of primary nocturnal enuresis in adolescents and adults

Study 45A03-008: Renal concentration capacity test: a comparison between Minirin© tablets and intranasal treatment, assessed in children as a night test

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 45A06-53: Long term double-blind, randomized multicentre study to compare two doses of desmopressin tablets in the management of primary nocturnal enuresis in adolescents and adults

Study 45A03-008: Renal concentration capacity test: a comparison between Minirin© tablets and intranasal treatment, assessed in children as a night test

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 68,471

YES

!

!

! NO

! Explain:

Investigation #2

IND # 68,471

YES

!

!

! NO

! Explain:

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

/s/

Theresa Kehoe

5/16/2008 04:46:20 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-795 Supplement Type (e.g. SE5): N/A Supplement Number: N/AStamp Date: September 27, 2007 PDUFA Goal Date: March 27, 2008HFD 510 Trade and generic names/dosage form: Minirin (desmopressin acetate) Tablets, 0.1 and 0.2 mgApplicant: Ferring Pharmaceuticals, Inc. Therapeutic Class: vasopressin analogue

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/AEach indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*Number of indications for this application(s): 2Indication #1: Management of primary nocturnal enuresis (PNE)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <5 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children (under 5 years of age)
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 5 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Renal Concentration Capacity Test (to determine the capacity of the kidney to concentrate urine)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 - No: Please check all that apply: Partial Waiver Deferred Completed
- NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. <u>0</u>	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. <u><3</u>	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 3 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Jennifer Johnson
3/27/2008 05:03:20 PM

Submitted March 2, 2005

20. Other

20.1. Pediatric Waiver

Ferring Pharmaceuticals Inc. requests a full waiver of the requirements for pediatric studies under 21 CFR 610.27 (c)(2). The justification for this request is provided below.

This 505(b)(2) application is for approval of MINIRIN Tablets for the following new indications:

- the test for renal concentrating capacity
- the treatment of primary nocturnal enuresis (PNE) in adults _____

b(4)

DDAVP Tablets (NDA 19-955, Aventis) are approved for the indication of PNE in pediatric patients age 6 years and older.

MINIRIN Tablets do not represent a meaningful therapeutic benefit over existing therapies for pediatric patients under 6 years of age and are not likely to be used in a substantial number of pediatric patients under 6 years of age.

APPEARS THIS WAY ON ORIGINAL

16. Debarment Certification

Ferring Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ronald T. Hargreaves
Ronald T. Hargreaves, Ph.D.
Executive Director
Regulatory Affairs

3/2/05
Date

APPEARS THIS WAY ON ORIGINAL

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

b(4)

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Ronald T. Hargreaves, Ph.D.	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION Ferring Pharmaceuticals Inc., 4 Gatehall Drive, Third Floor, Parsippany, NJ 07054	
SIGNATURE <i>Ronald T. Hargreaves.</i>	DATE 2/25/08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

19. Financial Disclosure Information

Ferring Pharmaceuticals Inc. is an affiliate of Ferring Holding S.A. The patent covering the composition and use of MINIRIN Tablets is owned by Ferring B.V., also an affiliate of Ferring Holding S.A. This group of companies is privately owned. Therefore, the investigators who carried out the clinical studies on which this application relies had no financial interest in the company and no proprietary interest in the tested product.

As required by 21 CFR 54, Financial Disclosure by Clinical Investigators, Ferring Pharmaceuticals Inc. is submitting certification on the financial interest of investigators who performed clinical studies included in this application. A completed Form FDA 3454 is attached.

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Ronald T. Hargreaves		TITLE Executive Director, Regulatory Affairs	
FIRM/ORGANIZATION Ferring Pharmaceuticals Inc., 400 Rella Blvd., Suite 300, Suffern, NY 10901			
SIGNATURE <i>Ronald T. Hargreaves</i>		DATE 02/28/2005	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

ACTION PACKAGE CHECKLIST

Application Information		
NDA # 21-795	NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: N/A Established Name: desmopressin acetate Dosage Form: tablets (0.1 and 0.2 mg)		Applicant: Ferring Pharmaceuticals, Inc.
RPM: Jennifer Johnson		Division: HFD-510 Phone # 301-796-2194
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) (This is the second review cycle for NDA 21-795.)		<p>NDA 19-955 for DDAVP (desmopressin acetate) Tablets: currently approved for the management of central diabetes insipidus (CDI) and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region, and for the management of primary nocturnal enuresis (PNE) in children six years of age and older – sponsor is sanofi-aventis</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Both DDAVP and Minirin are synthetic vasopressin (ADH) analogues that contain 0.1 and 0.2 mg of desmopressin acetate in a tablet formulation (Ferring is the manufacturer for both products). The sponsor proposes in this application to demonstrate bioequivalence between its product and the relied-upon approved product.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p>X Confirmed <input type="checkbox"/> Corrected Date: March 31, 2008</p>
❖ User Fee Goal Date ❖ Action Goal Date (if different)		March 27, 2008 May 8, 2008
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		Approvable (AE) letter issued December 22, 2005
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	X Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p>
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<p>X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<p>21 CFR 314.50(i)(1)(i)(A) X Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p>X No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) X Verified</p> <p>X Yes <input type="checkbox"/> No</p>

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

Note: The responses to the above five patent certification questions are correct for 4 of the 5 applicable patents in this application: 5047398, 5500413, 5674850, and 5763407. The applicant submitted a patent certification for patent 7022340 until March 18, 2008. This was a

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	<p><i>late-listed patent (i.e., the patent was issued on April 4, 2006, but the patent listing was not received by FDA until May 5, 2006). However, since the original application was submitted on March 2, 2005, and the patent listing submission was received after the first review cycle was completed (i.e., the application was approved on the second review cycle), the 45-day stay of approval does not apply.</i></p>
Summary Reviews	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>Clinical team leader memos: March 31, 2008 December 22, 2005</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	<p>N/A</p>
Labeling	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>April 3, 2008</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>April 24, 2008 (final labeling amendment)</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>March 2, 2005 (1st review cycle) and November 1, 2007 (2nd review cycle) N/A</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>N/A</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>N/A</p>
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>N/A</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>N/A</p>
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>Notified sponsor of Division acceptance of final agreed-upon labels on April 24, 2008</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>April 24, 2008 (final labeling amendment)</p>

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DMEDP March 21, 2008 <input checked="" type="checkbox"/> DMETS December 8, 2005 <input type="checkbox"/> DSRCS N/A <input type="checkbox"/> DDMAC N/A <input type="checkbox"/> SEALD N/A <input type="checkbox"/> Other reviews N/A <input type="checkbox"/> Memos of Mtgs N/A
---	--

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	June 2, 2005
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None N/A N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	March 26, February 25, 2008; November 30, 2007; December 13, 8, 2006; December 12, August 17, May 17, March 23, 2005
❖ Internal memoranda, telecons, email, etc.	Administrative split memo dated April 1, 2008
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	N/A <input checked="" type="checkbox"/> May 4, 2004 <input checked="" type="checkbox"/> No mtg End of Review: March 21, 2006
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting N/A N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	March 26, 2008 (#3) December 16, 2005 (#2) November 17, 2005 (#1)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	See CMC review (pp. 47-48) #1 dated November 17, 2005

• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: March 26, 2008 (2 nd cycle) and December 7, 2005 (1 st cycle) X Acceptable <input type="checkbox"/> Withhold recommendation
❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested X Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Not needed
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	X None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	March 20, 2008 (2 nd cycle) December 21, 2005 (1 st cycle)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	March 20, 2008
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	See pages 8-9 of clinical review dated March 20, 2008
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	X Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	N/A
• Bioequivalence Studies	March 17, 2008 (2 nd cycle) December 7, 2005 (1 st cycle)
• Clin Pharm Studies	N/A
❖ Statistical Review(s) (<i>indicate date for each review</i>)	X None needed
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	March 26, 2008 (2 nd cycle) December 16, 2005 (Addendum) November 30, 2005 (1 st cycle)

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
5/21/2008 05:24:47 PM

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, December 13, 2007 2:03 PM
To: 'ron.hargreaves@ferring.com'
Cc: Johnson, Jennifer
Subject: RE: NDA 21-795: Information Request

Dear Ron,

I hope that all is well with you.

I am writing to check in with you regarding the status of our outstanding request below, and to also add a request to send a desk copy of the NDA resubmission (if possible, as it would help our reviewers to have an extra copy).

I would appreciate it if you could send the desk copy to my attention at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
10903 New Hampshire Ave, Bldg 22
Room 3393
Silver Spring, MD 20993-0002

Please let me know if you have any questions.

Many thanks,
Jennifer

From: Johnson, Jennifer
Sent: Monday, December 03, 2007 11:48 AM
To: 'ron.hargreaves@ferring.com'
Cc: Johnson, Jennifer
Subject: RE: NDA 21-795: Waiver of Pediatric Studies and Information Request

Dear Ron,

Thanks so much for the information - we figured everything out and issued the acknowledgment letter on Friday, November 30th. It is attached to this email for your convenience. You do not have to submit anything further at this time (in regards to the waiver).

However, we do have a request from one of our reviewers:

Please send the electronic data for individual plasma concentrations and pharmacokinetic parameters of desmopressin used in the bioequivalence assessment as an official amendment to the NDA.

Let me know if you have any questions.

Many thanks,
Jennifer

Jennifer Johnson

5/13/2008

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: ron.hargreaves@ferring.com [mailto:ron.hargreaves@ferring.com]
Sent: Thursday, November 29, 2007 3:31 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-795: Waiver of Pediatric Studies

Dear Jennifer,

The request for a waiver of pediatric studies was provided in volume 1, page 91, of the original submission of the NDA. A copy of that page is provided below. I did not request a waiver in the resubmission, but if I need to do so I will send it this week.

Thanks and best regards,

Ron

From: Johnson, Jennifer [mailto:jennifer.johnson@fda.hhs.gov]
Sent: Wednesday, November 28, 2007 11:38 AM
To: Hargreaves, Ron
Cc: Johnson, Jennifer
Subject: NDA 21-795: Waiver of Pediatric Studies

Dear Ron,

I hope that all is well with you and that you had a wonderful Thanksgiving holiday.

I was just wondering if you had requested a waiver of pediatric studies with the NDA 21-795 resubmission. I was looking through volume 1 of the application and could not find it, so maybe I missed it. Could you pinpoint its exact location in the submission? Was a waiver requested for all 3 indications? If so, could you specify the age ranges for each?

Thanks so much for your help - it is greatly appreciated.
Once I have this information, I can issue the acknowledgment letter.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone

5/13/2008

301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

5/13/2008

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/s/

Jennifer Johnson
5/13/2008 03:33:05 PM
CSO

Email sent to sponsor on December 13, 2007

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, May 09, 2008 4:09 PM
To: CDER-APPROVALS
Cc: Johnson, Jennifer
Subject: Approval of NDA 21-795

Date of approval: May 8, 2008

NDA#: 21-795

Name of drug: desmopressin acetate tablets

Name of sponsor: Ferring Pharmaceuticals, Inc.

Indications:

- 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 management of primary nocturnal enuresis
- to determine the capacity of the kidney to concentrate urine in pediatric patients (Renal Concentration Capacity Test)

Dosage form: tablet

Route of administration: oral

Rx

Drug classification: 5

Review priority rating: S (standard)

Feel free to contact me if you require additional information.

Thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

5/9/2008

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, March 26, 2008 6:12 PM
To: 'ron.hargreaves@ferring.com'
Cc: Johnson, Jennifer
Subject: NDA 21-795: Minirin Tablets (Labeling Comments and Recommendations)
Attachments: DMEDP Comments to Sponsor 21795.pdf

Dear Ron,

Attached are the labeling comments and recommendations from the Division of Medication Error Prevention.

While the recommendations regarding the proprietary name list Niravam, Minerin, Minocin, Minitran, and Minirin Nasal Spray, the Division of Metabolism and Endocrinology Products is concerned with Niravam, especially with our knowledge of your ~~_____~~. We will discuss this during our teleconference tomorrow morning.

b(4)

Also contained in this document are recommendations for the PI and the carton and container labeling.

Please let me know if you have any questions or comments.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

3/31/2008

Johnson, Jennifer

From: Pian, Lee Ping
Sent: Tuesday, March 25, 2008 2:52 PM
To: Johnson, Jennifer
Cc: Sahlroot, Jon T
Subject: RE: Status of stats review for Minirin Tablets (NDA 21-795)

Jennifer,

Todd told me the original review which is in DFS under discipline BIOMETRICS and my name will do. We don't need to do stat review for this resubmission.

Please let me know if you have any questions.

Thanks,
lee

From: Johnson, Jennifer
Sent: Tuesday, March 25, 2008 2:14 PM
To: Pian, Lee Ping
Cc: Sahlroot, Jon T
Subject: Status of stats review for Minirin Tablets (NDA 21-795)

Hi Lee,

Just checking in on the status of the stats review for Minirin Tablets since goal date is this Thursday...

Thanks much,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

3/17/08

MEMORANDUM

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

DATE: March 17, 2008

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-795
MINIRIN® (desmopressin acetate) Tablets, 0.1 mg
and 0.2 mg, Sponsored by Ferring Pharmaceuticals

TO: Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
(OND/ODEII/DMEP)

At the request of DMEP; the Division of Scientific Investigations conducted an audit of the analytical portion of the following bioequivalence study:

Study Number: FE992026 CS28

Study Title: "An Open-labeled, Randomized, Two-sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6 mg Dose of MINIRIN® Tablets (3 x 0.2 mg) Compared to a Single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects"

The analytical portion _____ of Study FE992026 CS28 was conducted at _____
_____ Audit of the clinical portion of Study FE992026 CS28 was not requested.

b(4)

Following the inspection at _____, Form FDA-483 was issued (attachment 1). Our evaluation of the significant findings is as follows:

b(4)

Findings at _____

b(4)

1. The firm failed to maintain clear and adequate documentation for the following:
 - a. Verification that assay buffer, antibody, and the monoiodinated tracer (¹²⁵I-DDAVP) were added to dried extracts per the firm's method operating procedure
 - b. The actual incubation time of the reconstituted extracts with the antibody and tracer
 - c. The biological matrix used for subject sample dilutions
 - d. Storage conditions for the _____ suspension and _____ solution used during the study.

b(4)

Although the firm stated during the inspection that the method operating procedure (QA199, Final E02, "Quantitative Determination of Desmopressin in Human Plasma") was followed, there was no documentation verifying critical steps performed for the _____ (see 1(a) and 1(b)).

b(4)

K₃EDTA human plasma was used during pre-study validation of dilution integrity. However, the firm did not document the actual matrix used during the study when diluting subject samples.

Per the method operating procedure, the _____ suspension and _____ solution were to be stored at 5°C ± 3°C. However, the firm did not document the storage location of either reagent.

b(4)

Although the firm needs to improve their documentation practices, the above findings should not impact study outcome. Calibrators and QCs processed with the subject samples suggest adequate sample processing, and less than 0.5% of study samples required dilution.

During the inspection, the firm's management promised to implement corrective actions.

2. The firm failed to verify that samples were loaded on the gamma counter according to the sample analysis sequence file for all runs.

Page 3 of 5 - NDA 21-795, MINIRIN® (desmopressin acetate)
Tablets, 0.1 mg and 0.2 mg

For subjects 78 and 79, P1, 30 min samples (see attachment 2), the firm could not explain the aberrant values. Since the firm did not conduct sample sequence verification, a switching of samples could not be ruled out.

The firm needs to improve their documentation practices. During the inspection, the firm's management promised to implement corrective actions.

Conclusion:

Following our evaluation of the inspectional findings, DSI finds the accuracy of data from subjects 78 and 79 to be questionable, in light of the anomalous results for subjects 78 and 79 and the lack of investigation and sample sequence verification. The review division should consider this issue in their review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

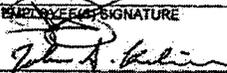
John A. Kadavil, Ph.D.

Final Classification:

cc:
OC DSI/RF
OC/Vaccari
OC DSI GLPBB/Kadavil/Himaya/CF
OND ODEII DMEP/Johnson (via DFS)
OTS OCP DCP2/Khurana (via DFS)
HFR-PA1530/Shrifter
Draft: JAK 3/14/08
Edits: JAO 3/14/08; MKY 3/17/08
DSI: — O:\BE\eircover\21795b_fer.des.doc
FACTS: —

b(4)

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER 1431 Harbor Bay Parkway Alameda, CA 94502 (510) 337-6700		DATE(S) OF INSPECTION 03 - 06 Mar 2008 FBI NUMBER	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: _____			
FIRM NAME _____		STREET ADDRESS _____	
CITY, STATE AND ZIP CODE _____		TYPE OF ESTABLISHMENT INSPECTED Bioanalytical Laboratory	
<p><small>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVES DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVES DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</small></p> <p>DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:</p>			
<p>In regards to the QA 504 study entitled: "An Open-Labeled, Randomized, Two-sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6 mg Dose of MINIRIN® Tablets (3 x 0.2 mg) Compared to a Single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects", Study number: FE992026 CS28, NDA 21-795, Sponsor: Ferring Pharmaceuticals:</p> <ol style="list-style-type: none"> 1) Failure to maintain clear and adequate documentation for the following: <ol style="list-style-type: none"> a) Verification that assay buffer, antibody, and the monoiodinated tracer (¹²⁵I-DDAVP) were added to dried extracts in accordance with the method operating procedure QA199, Final E02, "Quantitative Determination of Desmopressin in Human Plasma". b) The actual incubation time of the reconstituted extract with the antibody and tracer. c) The biological matrix used for the subject sample dilutions. For validation of dilutional integrity, _____ human plasma (from pooled plasma) was used. d) Storage conditions for the _____ suspension and the _____ solution which were used during the study. 2) Failure to verify that samples were loaded on the gamma counter according to the sample analysis sequence file for all runs. 			
SEE REVERSE OF THIS PAGE	INSPECTOR'S SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeffrey W. Shriffer, C.S.O. John A. Kadavil, Pharmacologist	DATE ISSUED 06 Mar 2008

b(4)

b(4)

Results Desmopressin [pg/mL]

Time point	Subject 78		Subject 79	
	Period 1	Period 2	Period 1	Period 2
Predose				
15 min				
30 min				
45 min				
1h				
1h15min				
1h30min				
2h				
3h				
4h				
5h				
6h				
8h				
10h				
12h				
14h				

bold: LFU; samples not interchanged at

Time point	Subject 80	
	Period 1	Period 2
Pre-dose		
15 min		
30 min		
45 min		
1h		
1h15min		
1h30min		
2h		
3h		
4h		
5h		
6h		
8h		
10h		
12h		
14h		

b(4)

b(4)

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/s/

John Kadavil

3/17/2008 02:02:04 PM

PHARMACOLOGIST

Dr. Martin K. Yau signed the paper copy on
3/17/08. Hard copies available upon request.

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, February 25, 2008 12:36 PM
To: 'ron.hargreaves@ferring.com'
Cc: Johnson, Jennifer
Subject: NDA 21-795: Information Request/Clarification

Dear Ron,

I hope that you had a good weekend.

We have a question regarding NDA 21-795, Minirin Tablets. Was the financial disclosure information for the investigator at the site for the PK study (FE 992026 CS28) in North Carolina included in the NDA resubmission? If so, we cannot seem to find it.

If it is not included, could you please send it both as an official amendment to the NDA and to me via email (to save time since we have one month left in the review cycle)? We would greatly appreciate your help.

Please let me know if you have any questions.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

Jennifer Johnson
5/13/2008 03:34:12 PM
CSO

Email information request to sponsor on February 25, 2008

REQUEST FOR CONSULTATION

☐ (Division/Office):

UNDER ROSE CONSULTS

FROM: Jennifer Johnson, Regulatory Project Manager,
HFD-510, WO22, Rm 3393

DATE February 21, 2008	IND NO. N/A	NDA NO. 21-795	TYPE OF DOCUMENT NDA Resubmission	DATE OF DOCUMENT September 24, 2007
NAME OF DRUG Minirin (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Vasopressin	DESIRED COMPLETION DATE March 20, 2008

NAME OF FIRM: Ferring Pharmaceuticals Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Please review again the acceptability of Minirin as a trade name. The DMETS trade name review (1st cycle, dated December 8, 2005) is available in DFS. The labeling for this NDA (draft package insert) was submitted electronically and is available in the EDR (revised carton and container labeling to be submitted officially very soon). Feel free to contact me with any questions or comments. Many thanks, Jennifer

PDUFA DATE: March 27, 2008

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 21-795

HFD-510/Division File

HFD-510/RPM

HFD-510/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER
Jennifer Johnson (301)-796-2194

METHOD OF DELIVERY (Check one)
 DFS ONLY MAIL HAND

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
2/21/2008 04:58:01 PM

11/30/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-795

Ferring Pharmaceuticals Inc.
Attention: Ronald T. Hargreaves, Ph.D.
Vice President, Regulatory Affairs
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054

Dear Dr. Hargreaves:

We acknowledge receipt on September 27, 2007, of your September 24, 2007, resubmission to your new drug application for Minirin (desmopressin acetate) Tablets, 0.1 and 0.2 mg.

We consider this a complete, class 2 response to our December 22, 2005, action letter. Therefore, the user fee goal date is **March 27, 2008**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request in this application for a waiver of pediatric studies for the renal concentrating capacity test and in children less than 6 years of age for the treatment of Primary Nocturnal Enuresis (PNE). An assessment of your request will be made during the review of the application.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-795

Ferring Pharmaceuticals, Inc.
Attention: Ronald Hargreaves, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Hargreaves:

Please refer to your new drug application (NDA) dated March 2, 2005, received March 4, 2005, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Minirin (desmopressin acetate) Tablets, 0.1 and 0.2 mg.

We also refer to the meeting between representatives of your firm and the FDA on February 21, 2006. This was an End of Review Conference to discuss the approvable action letter that issued on December 22, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Minutes from End of Review Conference held on February 21, 2006

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 21, 2006
TIME: 2:00 to 3:00 pm
LOCATION: White Oak Campus
APPLICATION: NDA 21-795
DRUG NAME: Minirin (desmopressin acetate) Tablets
TYPE OF MEETING: End of Review Conference

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Mary Parks, M.D.	Acting Director, Division of Metabolism and Endocrinology Products (DMEP)
Theresa Kehoe, M.D.	Acting Clinical Team Leader
William Lubas, M.D.	Clinical Reviewer
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
John Hill, Ph.D.	Chemistry Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Representatives of Ferring Pharmaceuticals Inc.

Marianne Kock	Senior Vice President, Global Regulatory Affairs
Ron Hargreaves	Executive Director, US Regulatory Affairs
Torben Balchen	Director, Clinical Pharmacology
Alf Carlshaf	Senior Director, Drug Bioanalysis and Metabolism

BACKGROUND:

On March 2, 2005, Ferring Pharmaceuticals submitted a 505(b)(2) NDA for Minirin (desmopressin acetate) Tablet. Desmopressin acetate is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. The sponsor was seeking approval for the following indications:

- antidiuretic replacement therapy in the management of central diabetes insipidus management of temporary polyuria and polydipsia following head trauma or surgery in the pituitary region
- to determine the capacity of the kidney to concentrate urine
- management of primary nocturnal enuresis in adults

The NDA application for Minirin Tablets is a 505(b)(2) and not a 505(j) application, because not all of the indications the sponsor is seeking have been approved and/or have been approved in the tablet dosage form to date. The two referenced NDAs are:

- NDA 19-776 for Concentraid® (desmopressin acetate) Intranasal Solution that was approved for RCCT and
- NDA 19-955 for DDAVP® (desmopressin acetate) Tablets that is approved for the treatment of PNE in children six years of age and older.

An approvable action letter was issued to the Sponsor on December 22, 2005, with the following deficiency:

An audit of the clinical and analytical portions of the bioequivalence study entitled, *An Open-Label, Randomized, Cross-over Study with Two Treatment Periods Investigating the Bioequivalence of a Single Dose of Minirin Tablets (0.2 mg) and a Single Dose of DDAVP Tablets (0.2 mg) in Healthy Male and Female Participants*" (FE992026 CS025) was conducted. The accuracy of a large number of analytical runs was not demonstrated due to unacceptable quality control performance. Before the application may be approved, it will be necessary for the Sponsor to conduct another bioequivalence study or re-run the stored samples from Study FE992026 CS025 with acceptable quality control performance.

The firm requested this End of Review Conference on December 30, 2005, and submitted questions via email on January 20, 2006, additional questions were brought to the meeting.

MEETING OBJECTIVES:

To discuss the deficiency and a response to that deficiency from the December 22, 2005, approvable action letter.

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

1. It appears that Ferring's response (dated December 16, 2005) to the FDA Form 483 issued on October 26, 2005 was not received in time to allow a review of its contents by the inspectors before the FDA action letter dated December 22, 2005. Taking into consideration our response to the 483, does the FDA still believe that the bioassay results for the study CS025 demonstrate unacceptable quality control performance?

The Sponsor's response, dated December 16, 2005, to the FDA Form 483 issued on October 26, 2005, has been reviewed by the Division of Scientific Investigations (DSI) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and the Agency still believes the bioassay results from study CS025 demonstrate unacceptable quality control performance.

- a. Would the old data be acceptable provided we re-analyze samples from CS025 with an updated, cross-validated analytical method with acceptable quality control performance? We have 1246 of 1855 samples left (67%).

OR

- b. Would demonstration of bioequivalence be accepted following re-analysis with an updated, robust method of the samples left from the study? Full profiles in both treatment periods are expected to be available for 36 of the 56 completing subjects.

The Sponsor needs to improve the assay and submit the assay validation data for review. If the assay validation is found acceptable, re-run the stored samples from Study FE992026 CS025. Number of subjects should be large enough to maintain statistical power for BE analysis. Otherwise, it will be necessary for the Sponsor to conduct another bioequivalence study. The key point is to improve the assay.

- c. If the new bioanalytical method (LLOQ 0.8 pg/mL) does not show the expected improvements, a new BE study will be performed with 80 subjects and using a bioanalytical method with a LLOQ of 5 pg/mL. Using a bioanalytical method with such a relatively high LLOQ results in not being able to measure 'complete' profiles. To minimize this effect, the highest approved dose of 0.6 mg (3 x 0.2 mg) will be administered. Based on PK modeling the observed area under the curve (AUC_t) of exposure is estimated to be above 80% of the total AUC for approximately 72% of individuals. Does the Division have any comments?

Response deferred until Sponsor makes the decision to conduct a new bioequivalence study instead of re-running stored samples.

2. In the action letter of December 22 it was stated that the labeling will be discussed at a later date. Is it likely that Ferring will receive approval for the new indication (RCCT) and the expanded indication (PNE in adults) requested in our NDA for MINIRIN Tablets?

The Division cannot comment on the approval status of an application in advance of the final action letter. After the Division has received a complete response to the December 22, 2005 approvable action letter, the contents of the Indications section of the labeling may be discussed.

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b(4)

Minutes prepared by: Lina AlJuburi
Chair concurrence: Mary Parks

APPEARS THIS WAY ON ORIGINAL

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/s/

Lina Aljuburi
3/21/2006 05:04:02 PM

ADDENDUM

NDA: 21-795
SUBMISSION DATE: MAR-02-2005
REVIEWER: Sang M. Chung, Ph.D.
TEAM LEADER: Hae-Young Ahn, Ph.D.

At the request of Clinical division, an audit was conducted by the Division of Scientific Investigations (DSI) to the bioequivalence study (FE992026 CS025). The DSI review recommended that desmopressin concentration data were not acceptable because of failure to assure accuracy of the analytical runs (refer the review in DFS by Dr. Sriram Subramaniam on December 7, 2005). According to the DSI review, at least 50% of the QCs at each concentration should be accurate to be acceptable, and the sponsor's results did not meet the standard. The sponsor set the criterion as $\frac{1}{2}$. Based on the DSI review, the OCP recommends as follows:

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It will be necessary for the sponsor to improve assay with acceptable quality control performance and rerun the stored samples from Study FE992026 CS025 or conduct another bioequivalence study with an improved assay.

APPEARS THIS WAY ON ORIGINAL

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/s/

Sang Chung
12/16/2005 03:19:12 PM
BIOPHARMACEUTICS

Hae-Young Ahn
12/16/2005 03:48:20 PM
BIOPHARMACEUTICS

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Monday, December 12, 2005 12:48 PM
To: 'ron.hargreaves@ferring.com'
Subject: NDA 21-795 Minrin (desmopressin acetate) Labeling Comments: Container and Carton

Hi, Ron

We have a few comments regarding your container and carton labels submitted in March 2 and April 27, 2005:

CONTAINER, UNIT DOSE BLISTER CARTON AND UNIT DOSE BLISTER LABEL

- Ensure the font size of the letters comprising the established name is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.
- Ensure the expression of strength is more prominent than the net quantity statement. The tablet strength needs to stand out more clearly on the label, as this is the only distinguishing mark between the 0.1 mg and 0.2 mg labels.
- Delete the dosage form statement “tablets” appearing with the strength and revise the established name to read as:
 desmopressin acetate tablets
- Ensure that child resistant closures are used for bottles intended to be a “unit of use” (e.g. 100 capsules) to be in accordance with the Poison Prevention Act.
- Delete the word “CAUTION” before Rx only.

Feel free to contact me if you have any questions regarding these comments.
Please email me revised carton and container labels.
You can expect comments on the package insert very soon.

Many thanks,
Lina

*Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)*

MEMORANDUM

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

DATE: December 5, 2005

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-795,
MINIRIN® (Desmopressin Acetate) Tablets,
Sponsored by Ferring Pharmaceuticals, Inc.

TO: David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology Drug
Products (HFD-510)

At the request of HFD-510, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Study: FE992026 CS025: "An Open-labeled, Randomized, Cross-over Study with Two Treatment Periods Investigating the Bioequivalence of a Single Dose of MINIRIN® Tablets (0.2 mg) and a Single Dose of DDAVP® Tablets (0.2 mg) in Healthy Male and Female Participants"

The clinical and analytical portions of the study were conducted at _____ and at Ferring's Drug Bioanalysis & Metabolism Department, Copenhagen, Denmark, respectively.

b(4)

Following the inspections at _____ (11/9-22/05) and Ferring's Drug Bioanalysis & Metabolism Department (10/24-26/05), Form 483s were issued. The objectionable items and our evaluation of them are as follows:

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Clinical Site: _____

b(4)

1) Failure to conduct the study as per the protocol.

- a) Subject #039 (W-C) failed to meet the inclusion criterion for Body Mass Index (BMI).

The subject's BMI (30.4 kg/m²) was outside the inclusion criterion (18-30 kg/m²) and should have been excluded. Nonetheless, the borderline BMI is not likely to affect the subject's data.

- b) Subject #46 (I-T) failed to meet the inclusion criterion for serum sodium level prior to dosing.

Subject #46 was dosed in Period II although the subject's serum sodium (147 mmol/L) was outside the normal range (135-145 mmol/L). In contrast, the clinic withdrew Subjects #033, #59 and #60 from the study due to abnormal sodium levels (2-3 mmol/L change from baseline). Subject #46 should have been excluded from the study.

- c) All the required follow-up examinations were not performed for Subjects #027 (DTD) and #033 (J-R) withdrawn from the study.

The site had no justification for not performing the follow-up tests. However, the finding does not affect the study as the subjects were withdrawn. Nonetheless, the clinic should assure subject safety.

- d) Plasma samples were not stored within 60 min of collection as required by the protocol.

The inspection found that samples were stored 65 to 80 min after collection.

Analytical Site: Ferring Pharmaceuticals A/s, Copenhagen, Denmark.

2) Failure to assure accuracy of the analytical runs.

The inspection revealed that the desmopressin radioimmunoassay did not perform well as evidenced by the very high rate of run failure, both during validation (58%) and study sample analysis (70%). In addition to the analytical runs rejected by Ferring (21 of 52: 40%), the inspection found that another 30%

(15) of the analytical runs (see Table 1) have failed and should have been rejected. The firm's criterion required only _____ of QCs at each concentration to be accurate (i.e. < 20% of the intended concentration). This criterion is not acceptable, as at least 50% of the QCs at each concentration should be accurate for a run to be acceptable. As indicated in Table 1, in several analytical runs less than 50% of QCs (i.e. 1 of 3) were accurate at one or more QC levels. Data from 45% (25 of 56) of the subjects enrolled in the study were affected in these runs.

b(4)

b(4)

Table 1

Analytical Run ID	Failed QC Level	Subjects Analyzed
100 084	100 pg/mL	#31, #32
100 085	100 pg/mL	#41, #42
100 091	36 & 100 pg/mL	#1, #2
100 093	100 pg/mL	#15, #16
100 094	36 pg/mL	#27, #28, #59
151 093	16 pg/mL	#51, #52
151 098	36 pg/mL	#19, #20
151 099	100 pg/mL	17 Repeats for #31, 41, 42, 44 & 45
154 071	2.4 pg/mL	#7, #8
154 077	16 pg/mL	#39, #40
154 079	36 pg/mL	#53, #54
154 082	16 pg/mL	#37, #38
154 086	100 pg/mL	#49, #50
154 089	100 pg/mL	#21, #22
192 002	36 pg/mL	#42 (P1)

Conclusion:

We recommend that the desmopressin concentration data for the study should not be accepted because the accuracy of a large number of analytical runs was not demonstrated due to unacceptable QC performance (Item 2).

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

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/s/

Sriram Subramaniam
12/7/2005 04:35:34 PM
PHARMACOLOGIST

Dr. Viswanathan signed the paper copy on 12/6/05. Paper
copies will be distributed to the cc: list.

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

MEMORANDUM

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

DATE: June 17, 2005

TO: Director, Investigations Branch
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

FROM: C.T. Viswanathan, Ph.D. *Michael Kelly for obob*
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2005, High Priority CDER User Fee NDA, Pre-Approval
Data Validation Inspection, Bioresearch Monitoring,
Human Drugs, CP 7348.001, PAC 48001A

RE: NDA 21-795
DRUG: Minirin[®] (Desmopressin Acetate) Tablets
SPONSOR: Ferring Pharmaceuticals, Inc..

This memo requests that you arrange for inspection of the clinical portion of the following bioequivalence study. Due to the User Fee deadline, this inspection should be completed by November 1, 2005.

Study Number: FE992026 CS025
Number: 66936

b(4)

Study Title: "An Open-labeled, Randomized, Cross-over Study with Two Treatment Periods Investigating the Bioequivalence of a Single Dose of MINIRIN[®] Tablets (0.2 mg) and a Single Dose of DDAVP[®] Tablets (0.2 mg) in Healthy Male and Female Participants"

Clinical Site:

b(4)

Clinical Investigator:

b(4)

Page 2 of 2: BIMO Assignment, NDA 21-795, sponsored by Ferring
Pharmaceuticals

Clinical Data Audit: Please check the batch numbers of both the test and the reference drug formulations used in the studies with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Following the identification of the investigator, background material will be forwarded directly. **A member of the Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301) 594-2043

cc:

HFD-45/RF

HFD-48/Skelly(2)/Himaya/CF

HFD-510/AlJuburi/NDA 21-795

HFR-CE250/Lynette Salisbury (please FAX copy to 410-779-5705)

Draft: MFS 6/17/05

DSI: ~~_____~~ O:\BE\assigns\bio21795c.doc

FACTS _____

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Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: P68,471
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) May 4, 2004 NO
If yes; distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 25, 2005

BACKGROUND: Minirin (desmopressin acetate) Tablets are a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. The sponsor is seeking approval for the following indications:

- (1) antidiuretic replacement therapy in the management of central diabetes insipidus management of temporary polyuria and polydipsia following head trauma or surgery in the pituitary region
- (2) to determine the capacity of the kidney to concentrate urine (RCCT)
- (3) management of primary nocturnal enuresis (PNE) _____

b(4)

The sponsor submitted this NDA as a 505(b)(2) application referencing two approved NDAs:

- (1) NDA 19-776 for Concentraid (desmopressin acetate) Intranasal Solution that was approved for RCCT – sponsor is Ferring, and
- (2) NDA 19-955 for DDAVP (desmopressin acetate) Tablets that is approved for the treatment of PNE in children six years of age and older – sponsor is Aventis.

The NDA application for Minirin Tablets is a 505(b)(2) and not a 505(j) application, because the indications the sponsor is seeking have not been approved and/or have not been approved in the tablet dosage form to date.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Mary Parks, Kati Johnson, William Lubas, John Hill, Stephen Moore, Sang Chung, Hae-Young Ahn, Lee-Ping Pian, Todd Sahlroot, Lina AlJuburi

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline

Reviewer

Medical:	William Lubas
Secondary Medical:	Mary Parks
Statistical:	Lee-Ping Pian
Pharmacology:	none needed
Statistical Pharmacology:	none needed
Chemistry:	John Hill
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sang Chung
Microbiology, sterility:	none needed
Microbiology, clinical (for antimicrobial products only):	none needed
DSI:	CT Viswanathan
Regulatory Project Management:	Lina AlJuburi
Other Consults:	DMETS

Per reviewers, are all parts in English or English translation?

YES NO

If no, explain:

CLINICAL

FILE

REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
 N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY N/A FILE REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Lina AlJuburi
Regulatory Project Manager, HFD-510

APPEARS THIS WAY ON ORIGINAL

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

APPEARS THIS WAY ON ORIGINAL

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 19-955 DDAVP (desmopressin acetate) Tablets and NDA 19-776 Concentraid (desmopressin acetate) Nasal Spray

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for two new indications: (1) Renal Concentration Capacity test, to determine the capacity of the kidney to concentrate urine. (2) Management of primary nocturnal enuresis (PNE) in adults.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): 5,500,413; 5,674,850; 5,763,407

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/

Lina Aljuburi

6/2/05 03:16:03 PM

CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-795

Ferring Pharmaceuticals, Inc.
Attention: Ronald Hargreaves, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Hargreaves:

Please refer to your March 2, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Minirin® (desmopressin acetate) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 3, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you submit the following information:

Chemistry, Manufacturing and Controls

1. Provide a description of and specify the differences between the punches and dyes used to manufacture the exhibit lots and the punches and dyes to be used for the proposed commercial US lots (volume 2, page 1).
2. Provide at least three months real-time and accelerated stability data in support of lots manufactured for American distribution using the final dyes and punches.
3. In your discussion of the stability data (section 3.2.P.8.3), we noted that the existing dissolution test method (QE-319) was refined to improve overall robustness (change paddle speed from 50 RPM to 75RPM). The new dissolution method (QE-333) was introduced into the ongoing stability study at the six month time-point. On page 177 you state that:

The dissolution results for the first 6 months are therefore only reported for information. Any results below the proposed dissolution limit for US (Q= — with the less robust method at 50 rpm, —, will therefore not be regarded as out-of-specification results, since the results do not reflect the quality of the tablet but artifacts in the dissolution method. It should be noted that testing to S3 was not conducted on any of the tests where Q= — failed.

b(4)

b(4)

Based on this statement, there appears to be no valid dissolution data for the first six months of the stability studies.

Clinical Pharmacology and Biopharmaceutics

4. Dissolution tests in three different conditions (e.g., 0.1 N HCl or simulated gastric fluid USP without enzymes; pH 4.5 buffer; and pH 6.8 buffer or simulated intestinal fluid USP without enzymes) need to be conducted to demonstrate that the dissolution condition you have chosen is optimal.
5. Comparative dissolution profiles between the clinical formulation and the to-be-marketed (TBM) formulation, using three different dissolution conditions, should be submitted from one batch from the TBM formulation and two batches from the clinical formulation. Similarity factors should be calculated.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Kati Johnson
5/17/05 03:38:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-795

Ferring Pharmaceuticals, Inc.
Attention: Ronald Hargreaves, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Hargreaves:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Minirin (desmopressin acetate) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	March 2, 2005
Date of Receipt:	March 4, 2005
Our Reference Number:	NDA 21-795

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 3, 2005, in accordance with 21 CFR 314.101(a). If this application is filed, the user fee goal date will be January 4, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies in patients less than 6 years of age for the treatment of Primary Nocturnal Enuresis (PNE) in this application. An assessment of your request will be made during the review of the application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

NDA 21-795

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Lina Aljuburi
3/23/05 03:18:18 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

APPLICANT'S NAME AND ADDRESS		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021795
Serrano Pharmaceuticals Inc. 100 Rella Blvd. Suite 300 Buffery, NY 10901		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
TELEPHONE NUMBER (Include Area Code) 845) 770-2600		
PRODUCT NAME MINIRIN (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg		6. USER FEE I.D. NUMBER 4923

RECEIVED
MAR 07 2005
FDR/CDER

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- | | |
|--|---|
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) | <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
BER, HFM-99
101 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Ronald T. Hargreaves

TITLE

Executive Director, Regulatory Affairs

DATE

28 February 2005



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,471

Hurley Consulting Associates Ltd.
Attention: Susan M. Mondabaugh, Ph.D.
Vice President of Regulatory Affairs
One Main Street
Chatham, NJ 07928

Dear Dr. Mondabaugh:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Minirin® (desmopressin acetate) Tablets.

We also refer to the meeting between representatives of Ferring Pharmaceuticals A/S, your firm and the FDA on May 4, 2004. The purpose of the meeting was to discuss the New Drug Application (NDA) submission for Minirin® (desmopressin acetate) Tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes for PreNDA meeting held on May 4, 2004

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Tuesday, May 4, 2004
TIME: 9:30 to 10:00 am
LOCATION: Parklawn Conference Center, Room "K"
APPLICATION: PIND 68,471
DRUG NAME: Minirin® (desmopressin acetate) Tablets
TYPE OF MEETING: Type B; PreNDA

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, M.D.	Director, Office of Drug Evaluation II
David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Mary Parks, M.D.	Deputy Director, DMEDP
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Eric Duffy, Ph.D.	Director, Division of New Drug Chemistry II
Chien-Hua Niu, Ph.D.	Chemistry, Manufacturing, and Controls Reviewer
Lee-Ping Pian, Ph.D.	Statistics Reviewer
Enid Galliers	Chief, Project Management Staff, DMEDP
Lina AlJuburi, Pharm.D.	Regulatory Project Manager, DMEDP

EXTERNAL CONSTITUENT ATTENDEES:

Ferring Pharmaceuticals A/S

Jens Peter Norgaard, M.D., DMSc.	Executive Director, Urology, Department of Medical Science
Anders Riis, M.Sc.	Project Statistician, Global Biometrics
Marianne Kock, M.Sc., M.B.A	Senior Vice President, Global Regulatory Affairs
Martin Hedenfalk, M.Sc.	Project Director, Global Regulatory Affairs
Asa Rembratt, M.Sc., Ph.D.	Clinical Research Scientist

b(4)

BACKGROUND:

Minirin® (desmopressin acetate) Tablets are a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. The sponsor is seeking approval for the following indications:

- use as a test of renal concentrating capacity (RCCT), and
- treatment of primary nocturnal enuresis (PNE) in children six to 17 years of age, adolescents above age 17 and adults.

The sponsor intends to submit this NDA as a 505(b)(2) application referencing two approved NDAs:

- NDA 19-776 for Concentraid® (desmopressin acetate) Intranasal Solution that was approved for RCCT – owned by Ferring, and
- NDA 19-955 for DDAVP® (desmopressin acetate) Tablets that is approved for the treatment of PNE in children six years of age and older – owned by Aventis.

The NDA application for Minirin® Tablets would be a 505(b)(2) and not a 505(j) application, because the indications the sponsor is seeking have not been approved and/or have not been approved in the tablet dosage form to date.

The firm requested a PreNDA meeting on March 12, 2004, and submitted the background package on April 2, 2004.

MEETING OBJECTIVES:

- To discuss the sponsor's plan to submit a 505(b)(2) NDA for Minirin® Tablets for the two indications: (1) use as a diagnostic test of renal concentrating capacity and (2) treatment of primary nocturnal enuresis in children six to 17 years of age, adolescents above age 17 and adults.
- To discuss the format and content of the NDA submission.

DISCUSSION POINTS:

1.1 CMC

Will the Division allow reference be made to NDA 19-955, since other than product identification markings the tablets are the same, in place of submitting a complete CMC section in the NDA?

If the sponsor has right of reference from Aventis to NDA 19-955, then the Division will refer to NDA 19-955 for the CMC section. However, without right of reference, a complete CMC section is required in the NDA submission. Of note, the sponsor manufactures DDAVP® Tablets for Aventis. Therefore, the sponsor does not anticipate any problem with submitting a complete CMC section in the NDA.

1.2 Pharmacology/Toxicology/Pharmacokinetics

The 505(b)(2) NDA would refer to approved NDA 19-955 (DDAVP® Tablets) for nonclinical pharmacology and toxicology data. Please confirm that this will be acceptable.

This will be acceptable.

1.3 Clinical

1.3.1 RCCT Indication

- The 505(b)(2) NDA would refer to approved NDA 19-955 (DDAVP® Tablets) for clinical pharmacology and clinical safety data. Please confirm that this will be acceptable.
- In addition, the application would also refer to NDA 19-776 for efficacy and safety data of desmopressin acetate as a renal concentration capacity test (Concentraid® Intranasal Solution). Please confirm that this would be acceptable even though the product was discontinued in June of 2000.
- It is planned that the instructions for performing the RCCT test will state that although the test can be performed at any time, conducting the test at night provides both patient convenience and the greater concentration capacity results. Please confirm that based on final review of the NDA, the Division agrees that this would be reasonable for inclusion in the package insert.
- Does the Division agree that the results of Study 45A03-008 will support the non-inferiority of desmopressin tablets to the nasal spray in measuring Renal Concentrating Capacity and the 505(b)(2) application?
- Does the Division agree that current reference levels of urine osmolality in children can be used also for evaluating the renal concentrating capacity test performed with desmopressin tablets?
- _____
- Does the Division agree that the data proposed for inclusion in the NDA (either directly or by reference) will be sufficient to support substantive review and possibly approval of desmopressin tablets as a diagnostic test in patients with need for evaluating renal concentrating capacity?

b(4)

1.3.2 PNE Indication

- The 505(b)(2) NDA would refer to approved NDA 19-955 (DDAVP® Tablets) for clinical pharmacology and clinical safety data for the approved indication of PNE. Please confirm that this will be acceptable.

1.5 Integrated Summary of Safety Information

The detailed table of contents and the draft plan for the pooling of safety data for the integrated summary of safety is included in the briefing book. Please confirm that this is acceptable to the Division.

The proposal for the integrated summary of safety is acceptable.

1.6 Integrated Summary of Effectiveness

The detailed table of contents for the integrated summary of effectiveness is included in the briefing book. There is no plan to pool the efficacy information. Please confirm that this is acceptable to the Division.

The proposal for the integrated summary of effectiveness is acceptable.

1.7 Financial Disclosure

The information on financial disclosure will be submitted in conformity with 21 CFR Part 54. Please confirm that this is acceptable to the Division.

This is acceptable.

1.8 Pediatric Exclusivity

Because DDAVP is indicated for use in children, a pediatric waiver will be requested. Please confirm that this is acceptable to the Division.

If an indication can be approved for PNE and RCCT in the pediatric patient population, the Division would consider the pediatric requirements fulfilled. However, a waiver request will be required for children less than six years of age for the PNE indication.

NOTE: The sponsor was notified that the 505(b)(2) paradigm is under active discussion within the Agency. The responses, listed above, are applicable to 505(b)(2) as of the date of this PreNDA meeting and regulations may be modified by the time this NDA is submitted.

POSTMEETING COMMENTS TO THE SPONSOR FROM THE OFFICE OF DRUG SAFETY (ODS):

ODS has completed its review of the Minirin® Tablets PreNDA background package and determined that there are no risk management issues identified in the package at this time. ODS has the following comments and recommendations.

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

RiskMAPs

2.5.5 Overview of Safety with appropriate cross references to section

2.7.4 Summary of Clinical Safety

and any other relevant sections of the Common Technical Document for the NDA/BLA application.

Pharmacovigilance plans

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4

Other Clinical Study Reports or other sections as appropriate

(e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/guidance/5766dft.pdf> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc>.
- If there is any information on product medication errors from the pre-marketing clinical experience, ODS requests that this information be submitted with the NDA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Minutes Preparer: Lina AlJuburi

Chair Concurrence: David Orloff

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this page is the manifestation of the electronic signature.**

/s/

Lina Aljuburi
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