CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-933
20-636/SE1-009

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Boehringer Ingelheim

Facsimile Cover Sheet

To: Mr. David Staten, RMO,
Company: FDA, CDER, Division of Antiviral Drug Products
Phone: 301 827 2335
Fax: 301 827 2523

From: Kevin Dransfield
Department: Drug Regulatory Affairs
Phone: 203 791 6242
Fax: 203 791 6262

Date: 09/08/98
Pages including cover page: 3

Comments:

Reference is made to the facsimile correspondence from Dr. Teresa Wu and Dr. Vanitha Sekar dated September 4, 1998 concerning Phase IV Commitments and Labeling Comments for the VIRAMUNE® oral suspension NDA 20-933 and the pediatric supplement (S-009) to NDA 20-636. Reference is also made to a telephone conversation between Dr. Wu, Ms. Christine Kelly, and members of Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) on September 4, 1998.

I. Phase IV commitments

FDA has requested that BIPI address four issues as Phase IV commitments in a complete study report for clinical trial ACTG 245. During the telephone conversation on September 4, it was discussed that BIPI will not prepare a BIPI-authored, formal clinical trial report for ACTG 245. Rather, BIPI commits to providing the Agency with the Executive Summary of this trial, as prepared by the ACTG. If any of the following four issues are not addressed adequately in the Executive Summary, BIPI will collaborate with the ACTG to perform additional analyses to meet FDA's requests, provided this

information is readily available in the ACTG database. The four issues outlined by FDA in the facsimile correspondence of September 4, and the response from BIPI, are discussed further below:

1. *The efficacy of the double- and triple-regimen of nevirapine as measured by changes of surrogate markers over 48 weeks.*

BIPI response: The Executive Summary report for ACTG 245 will address this issue.

2. *The appropriateness of a 2-week lead-in-dosing schedule as assessed by the incidence of rash events.*

BIPI response: The Executive Summary for ACTG 245 will provide an analysis of the incidence of adverse events in the Skin and Appendages body system in nevirapine treated patients versus controls. The nevirapine-attributable rate of these events can be compared to that in pediatric trial BI 882 (ACTG 180) in which a 4-week lead-in was utilized, and to previously submitted adult data, to confirm that the 2-week lead-in period for pediatric patients is sufficient.

3. *The characteristics of rash occurrence in children including the onset and accompanied symptoms and signs (such as allergic reactions).*

BIPI response: It is not yet known whether the analysis of rash in the Executive Summary will adequately address this issue. If the characteristics of rash in the study population are not adequately described, BIPI will collaborate with the ACTG to provide further analyses from the clinical trial database to address this issue. Since adverse event information in an Executive Summary is generally presented by body system, the number of patients with allergic reactions may not be specifically described.

4. *The incidence of hepatic adverse events and the significance of the alkaline phosphatase level elevations in the study population.*

BIPI response: The Executive Summary will provide an analysis of the incidence of hepatic events in nevirapine treated patients versus controls. If the Executive Summary does not adequately address the incidence of alkaline phosphatase abnormalities, BIPI will collaborate with the ACTG to provide further information as collected in the clinical trial database.

II. Biopharmaceutical comments on VIRAMUNE® package insert:

BIPI agrees to incorporate the changes to the labeling as suggested by the Agency. These comments have been incorporated into the draft labeling submitted by facsimile to the Agency on September 4, 1998.

If you have any questions or comments regarding this correspondence, please contact me at either of the two numbers listed below. A final commitment letter will be prepared pending the Agency's comments on this correspondence.

Sincerely,

Kevin Dransfield

Kevin Dransfield
Manager, Drug Regulatory Affairs
Telephone: 203 791-6242
Telefax: 203 791-6262

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Martin M. Kaplan, M.D., J.D.

3. TELEPHONE NUMBER *(Include Area Code)* (203) 798-4486

4. PRODUCT NAME VIRAMUNE® Tablets, 200 mg

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?? [X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

3425

7. LICENSE NUMBER/NDA NUMBER

NDA 20-636 /S-009

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

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

[ ] AN INSULIN PRODUCT SUBMITTED UNDER 506

[ ] THE APPLICATON IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)

[ ] THE APPLICATON IS SUBMITTED UNDER 505(b)(2)

FOR BIOLOGICAL PRODUCTS ONLY

[ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

[ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

[ ] A CRUDE ALLERGENIC EXTRACT PRODUCT

[ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? [ ] YES [X] NO (See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO (See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Pamela S. Strode	Senior Associate Director, Drug Regulatory Affairs	March 13, 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Martin M. Kaplan, M.D., J.D.

3. TELEPHONE NUMBER *(Include Area Code)* (203) 798-4486

4. PRODUCT NAME VIRAMUNE® (nevirapine) Oral Suspension 50 mg/5mL

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

3434

7. LICENSE NUMBER/NDA NUMBER

NDA 20-933

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATON IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATON IS SUBMITTED UNDER 505(b)(2)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO (See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO (See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Patricia Watson Patricia Watson	DRA Technical Director Drug Regulatory Affairs	April 15, 1998

FORM FDA 3397 (12/93)

DEBARMENT CERTIFICATION

SECTION 306(k)(2) OF THE ACT
21 U.S.C.335a(k)(1)

The undersigned certifies, that, to the best knowledge and belief of the undersigned, Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with VIRAMUNE® (nevirapine) Oral Suspension.

Signature

Name of the Applicant: Martin Kaplan, M.D.
Vice-President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

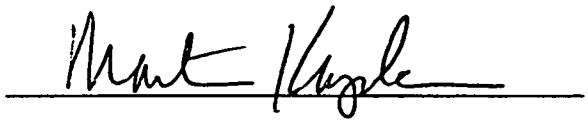
Mailing Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

CERTIFICATION REQUIREMENT

—

SECTION 306(k)(2) OF THE ACT
21 U.S.C.335a(k)(1)

The undersigned certifies, that, to the best knowledge and belief of the undersigned, Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with VIRAMUNE® Tablets.

Signature 

Name of the Applicant: Martin Kaplan, M.D.
Vice-President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Mailing Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

The following is the patent information required to be submitted under 21 CFR 314.53:

(i)	Applicable Patent Numbers and Expiration Date of Each	U.S. Patent No. 5,366,972 November 22, 2011
(ii)	Type of Patent	Drug substance, drug product and method of use
(iii)	Name of Patent Owner	Boehringer Ingelheim Pharmaceuticals, Inc. and Dr. Karl Thomae GmbH, as joint owners
(iv)	Entity 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 C.F.R §§ 314.52 and 314.95	Boehringer Ingelheim Pharmaceuticals, Inc.(the applicant), which has its place of business at 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877

EXCLUSIVITY SUMMARY for NDA # 20-636 SUPPL # SE1-009

Trade Name VIRAMUNE® **Generic Name** Nevirapine Tablets

Applicant Name Boehringer Ingelheim Pharmceuticals **HFD-**530

Approval Date September 11, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?
   YES /_/ NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO /_/

   If yes, what type? (SE1, SE2, etc.) SE1

   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 /X/

   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.

   _____

   _____

   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:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

cc: Original NDA
Division File
HFD-83/ Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__/ NO /X/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X__/ NO /___/

If yes, NDA # 20-636 Drug Name VIRAMUNE®

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 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. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

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 # ____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain: _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ 9/3/98

Signature Date

Title: Medical Officer

/S/ 9/11/98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA
Division File
HFD-85/Mary Ann Holovac

EXCLUSIVITY SUMMARY for NDA # 20-933 SUPPL # _____

Trade Name VIRAMUNE® **Generic Name** [redacted]

Applicant Name Boehringer Ingelheim Pharmceuticals **HFD-530**

Approval Date September 11, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?
   YES /X/ NO /_/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X_/

   If yes, what type? (SE1, SE2, etc.) ____

   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 /X/

   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.

   THIS NDA INCLUDES ONLY THE INFORMATION ON CHEMISTRY, MANUFACTURING & CONTROL OF THE DRUG PRODUCT

   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:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

cc: Original NDA
Division File
HFD-~~30~~7 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X_/ NO /_/

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

___3___

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

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 /_X__/ NO /___/

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

NDA # 20-636 VIRAMUNE®

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 /_X__/

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. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 /___/

APPEARS THIS WAY
ON ORIGINAL

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:

Investigation #1, Study # ACTG 180

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

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 /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #_, Study # ACTG 180

Investigation #_, Study # _____

Investigation #_, Study # _____

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 ~~____~~ 3 / ✓ NO /___/ Explain: _____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain: _____

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

/S/ 9/3/98

Signature Date

Title: Medical Officer

/S/ 9/11/98

Signature of Division Director Date

cc: Original NDA
Division File
HFD-85/Mary Ann Holovac

1) The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., believes that after approval of the New Drug Application, VIRAMUNE® (nevirapine) Oral Suspension, 50 mg/5mL will be entitled to a period of marketing exclusivity under the provisions of 21 CFR 314.108, and is, therefore, claiming exclusivity.

2) Reference is made to 21 CFR 314.108(b)(4) to support the applicant's claim to exclusivity for VIRAMUNE® (nevirapine) Oral Suspension, 50 mg/5mL.

3) The applicant claims and is entitled to a period of 3 years of exclusivity under 21 CFR 314.108(b)(4) because:

(i) This application was submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

(ii) This application will be approved after September 24, 1984.

(iii) This application is for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the Federal Food, Drug and Cosmetic Act. Namely, the sole active moiety in the drug for which the applicant is seeking approval, VIRAMUNE® (nevirapine) Oral Suspension, 50 mg/5mL, is nevirapine, the chemical name for which is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one. A drug containing nevirapine as an active moiety (VIRAMUNE® Tablets) has previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act (under NDA Number 20-636).

(iv) This application is based on reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that will be essential to approval of the application.

FROM ORIGINAL NDA 20-636

13.0 PATENT INFORMATION

1)	Name of Drug Product	VIRAMUNE®
2)	Active Ingredient(s)	nevirapine (the chemical name for which is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one)
3)	Strength(s)	200 mg
4)	Dosage Form	tablet
	Route of Administration	oral
5)	Name of Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
6)	NDA Number	20-636
7)	Applicable Patent Numbers and Expiration Date of Each	U.S. Patent No. 5,366,972 November 22, 2011
8)	Type of Patent	drug, drug product and method of use
9)	Name of Patent Owner	Boehringer Ingelheim Pharmaceuticals, Inc. and Dr. Karl Thomae GmbH, as joint owners

10) Declaration

The undersigned declares that Patent No. 5,366,972 covers the formulation, composition, and/or method of use of Viramune. This product is the subject of this application for which approval is being sought.

By: 

Alan Stempel

Capacity: Attorney for Patent Owner and Applicant

Date: October 20, 1995

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-636 Supplement # 009 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: VIRAMUNE (nevirapine) Tablets Action: (AP) AE NA

Applicant Boehringer Ingelheim Therapeutic Class Non-nucleoside reverse transpcriptase inhibitor

Indication(s) previously approved HIV infection in adults used in Combination with other antiretrovirals.
Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Indication in this application pediatric use (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/
Signature of Preparer and Title

Sept 3, 1998
Date

cc: Orig NDA/PLA/PMA # N 20-636
HFD 530 /Div File 20-636
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/3/98)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-933 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: VIRAMUNE (nevirapine) oral suspension 50 mg/mL Action (AP) AE NA

Applicant Boehringer Ingelheim Therapeutic Class Non-nucleoside reverse transpcriptase inhibitor

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ _____ Sept 3, 1998

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # N 20 - 933
HF D 530 /Div File 20-933
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/3/98)

Group Leader's Memo **Sept. 4, 1998**

NDA 20-636, VIRAMUNE tablet
NDA 20-933, VIRAMUNE oral suspension

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Drug: Viramune (nevirapine)
200 mg tablets and oral suspension (50 mg/5mL)

NDA 20-636 is a supplement that provides pharmacokinetic, safety and limited activity data in support of pediatric dosing recommendations and a pediatric use statement in the nevirapine package insert. NDA 20-933 includes data to support an approval of a new formulation, an oral suspension, with intended use for pediatric patients. I concur with the clinical, biopharmaceutics, and chemistry reviewers' conclusions that the data submitted support the approvals of the oral suspension formulation of nevirapine and nevirapine label revisions for pediatric dosing recommendations and use.

The dosing regimen recommendations are primarily supported by safety and pharmacokinetic data from 37 pediatric patients ranging in age from 1 month to 18 years (Study 882). Similar types of data have been used to support pediatric use and dosing for other antiretroviral drugs in this age range. Based on the PK data from this study, the pediatric dosing regimens are predicted to achieve nevirapine steady-state concentrations similar to that observed in adults receiving the approved dose. Please see Dr. Sekar's review (Biopharmaceutics) for details regarding the dosing regimen. Overall, safety data from these 37 patients and limited adverse event data from ACTG study #245 indicate that the adverse event profile for nevirapine is similar in children and adults. Rash and severe rash occurred at a similar frequency. Granulocytopenia appeared to occur with a greater frequency in children but this may have been related to the concomitant use of ZDV. Safety and pharmacokinetic data for the use of nevirapine in neonates are still needed.

/S/

Jeffrey S. Murray M.D., M.P.H.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: June 25, 1997

IND: [redacted]

Drug: Viramune (nevirapine)

Sponsor: Boehringer Ingelheim

Indication: Treatment of HIV

Type of Meeting: Pre-NDA

FDA Attendees:

David Feigal, M.D., M.P.H., Director, Office of Drug Evaluation IV
Donna Freeman, M.D., Acting Director, Division of Antiviral Drug Products
Walla Dempsey, Ph.D., Acting Deputy Director, Division of Antiviral Drug Products
Rachel Behrman, M.D., M.P.H., Medical Team Leader
John Martin, M.D., Medical Officer
Therese Cvetkovich, M.D., Medical Officer
George Lunn, Ph.D., Chemistry Reviewer
Gene Holbert, Ph.D., Chemistry Reviewer
Narrayana Battula, Ph.D., Reviewing Microbiologist
Vanitha Sekar, Ph.D., Reviewing Pharmacokineticist
Chandra Sahajwalla, Ph.D., Acting Team Leader for Biopharmaceutics
Jim Farrelly, Ph.D., Pharmacology Team Leader
Mike Elashoff, Ph.D., Biometrics Reviewer
Terrie Crescenzi, R.Ph., Regulatory Management Officer

External Constituents:

Dan Cotton, Sr. Assoc. Statistician, Biometrics and Data Management
Paul Gagnier, M.D., Clinical Research
Pam Strode, Sr. Assoc. Director, Drug Regulatory Affairs
Mike Lamson, Ph.D., Principal Scientist, DMPK
James Kearns, Ph.D., Director, Drug Metabolism and Pharmacokinetics

Background:

This meeting was held at the request of the sponsor, submission dated June 5, 1997, to discuss clinical and pharmacokinetic issues relevant to the proposed pediatric supplement to NDA 20-636.

Viramune (nevirapine) Tablets, 200mg (NDA 20-636), is currently approved for use "in combination with nucleoside analogues for the treatment of HIV-1 infected adults who have experienced clinical and/or immunologic deterioration."

Nevirapine has been studied in pediatric patients since the clinical program was initiated in 1991. Boehringer Ingelheim now has activity, safety, and pharmacokinetic data available from the pediatric patient population for submission as part of a Supplement to NDA 20-636. The study report for the pivotal study 1100.882 will include pharmacokinetic, safety, tolerance and activity data of nevirapine alone and in double or triple combinations with nucleoside analogues. Supportive pharmacokinetic and safety data is intended to be provided from the following studies: single dose Study 1100.853; long term follow-up Study 1100.892 (with patients rolling over from Study 1100.882, providing > 4 years of safety data); Study ACTG 245 (a large ongoing pediatric study); and treatment protocol 1100.859 (expanded access).

Reference is made to the June 5, 1997 General Correspondence/Pre-NDA Background Package submission that contained the briefing document and discussion items for the Pre-NDA meeting.

Objective:

- Discuss the data package intended to support a proposed revision to the current labeling for Viramune.

Assessment:

The major clinical points expressed by the FDA clinical reviewers are as follows:

- As currently proposed, unblinded safety data on 37 subjects would most likely be inadequate to support inclusion of a pediatric usage statement in the package insert. Additional unblinded safety data would be needed to support this application. The inclusion of unblinded safety data from the ACTG 245 study appears to be adequate to support this application.

- We would want to see CRF's for all deaths and for all drop-outs from Study 882. From ACTG 245, we would want to see CRF's for all drug-related deaths, for all rashes greater than or equal to grade 2 in severity and, potentially, for a sample of and for all serious adverse events.

Discussion:

<u>Questions received in June 23 fax:</u>

1. In the summary of the multiple dose pediatric study (1100.882), it states that "majority of the

patients in this study received Nevirapine in the form of suspension; the total daily dose ranged from 120-240 mg/day". Please clarify the number of patients who were given the suspension, the duration of treatment and the dosing regimen that was used in the study.

The number of patients who received suspension, and the various dosing regimens used in this study will be clarified and described in detail by the sponsor in the NDA Submission.

2. Please clarify the dosing regimen used in the pediatric population with respect to the issue of autoinduction. [In adults, Nevirapine is dosed as 200 qd for 2 weeks followed by 200 mg bid].

The sponsor stated that the dosing regimen in children would address the issue of autoinduction (i.e. 120mg/m^2 QD for 2 weeks, followed by 120mg/m^2 BID).

3. Please indicate whether the suspension and the marketed tablet formulation are intended to be used interchangeably.

The sponsor stated that the two formulations were to be used interchangeably. They stated that the observed 18% reduction in AUC and Cmax values for the suspension compared to the tablet was largely attributable to the 11% residual drug remaining in the dosing cup following dosing of the suspension.

4. Please specify the formulation and strength of the suspension that will be used commercially. Study 1100.882 (multiple dose pediatric study) used a 5 mg/ml suspension. Also, please indicate whether the same formulation and strength were used in Study 1100.896 (bioavailability study) and Study 1100.1213 (bioequivalence study).

The sponsor stated that the formulations of the two suspensions differed only in concentration. Study 1100.896 used a 5mg/ml concentration, and study 1100.1213 used a 10mg/ml concentration. The FDA commented that study 1100.1213 would not support bioequivalence or interchangeability, based on the data available to us at present.

5. The following information with respect to the pharmacokinetic modeling should be submitted with the NDA package for review:

* A description of the NONMEM model building steps
* A table listing the different models tested with the objective function and variance
* Control files that were used, especially for the final pharmacokinetic model
* ASCII files of the data in NONMEM format
* Data as hard copy

The sponsor stated that the 812 NONMEM data is available.

6. Please consider evaluating the utility of using body weight for determining dosing, as this method of dosing may be easier to use rather than dosing by body surface area (BSA).

The sponsor stated that BSA is the preferred method. The FDA postulated that the

average practitioner may not be comfortable with BSA and requested the following:

- **Provide any examples where a commonly used drug is dosed by BSA**
- **Provide any information available about the general comprehension of BSA**
- **Review the data to ascertain whether dosing by weight is a realistic possibility**
- **Review the data to ascertain whether both BSA and weight adjusted dosing would be feasible. The FDA suggested the sponsor address whether they believe the average practitioner was comfortable using BSA.**

The sponsor was receptive to these recommendations.

Background Package Questions

1. Is the proposed dosing recommendation considered appropriate?

   FDA stated this is a review issue and could not comment at this time.

2. Is the proposed no age limit appropriate for labeling?

   FDA commented that this is also a review issue; the age ranges specified in the label would be a function of what ages have been investigated. If there are no data for a certain age range, the package insert will reflect that information.

3. Is the proposed format acceptable?

   FDA stated the format appears to be acceptable.

4. Is the proposed approach for providing case report forms acceptable?

   See above.

5. Will there be any electronic data required at the time of the submission?

   FDA stated that bioequivalence and bioavailability data would be requested.

6. If these data coincide with the availability of the adult clinical endpoint data to be submitted in support of traditional approval, would you prefer that these data come as one supplement to the NDA with one proposed revision to the labeling, or would you prefer these data to be captured in two supplements?

   FDA stated that the proposed pediatric supplement and the anticipated supplement aimed at obtaining traditional approval will need to be separate. However, it is our strong preference to review these supplement concurrently and, therefore, to undertake a single revision of the package insert. FDA also stated that if the application for traditional approval includes only data from studies that were part of the accelerated approval

package, this supplement may not trigger a user fee.

Signature, minutes preparer: _____ **Date:** _____
Conference Chair (or designated signatory): _____ **Date:** _____

Attachment/Handouts: 1

Attendance Roster

Concurrence:
HFD-530/ADivDir/Freeman
HFD-530/ADepDivDir/Dempsey
HFD-530/MTL/Behrman-13Jul97
HFD-530/MO/Martin-10Jul97
HFD-530/Biopharm/Sekar-9Jul97
HFD-530/CSO/Crescenzi-1Jul97

cc:
Original
Division file
HFD-530/Feigal
HFD-530/Freeman
HFD-530/Dempsey
HFD-530/Behrman
HFD-530/Martin
HFD-530/Cvetkovich
HFD-530/Farrelly
HFD-530/Sahajwalla
HFD-530/Sekar
HFD-530/Lunn
HFD-530/Holbert
HFD-530/Battula
HFD-530/Elashoff
HFD-530/Crescenzi

Meeting Minutes

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 4, 1998

To: Kevin Dransfield

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
Fax-203-791-6262

From: Teresa Wu, M.D., Ph.D., Medical Officer
Vanitha Sekar, Ph.D., Clinical Pharmacology and Biopharmaceutical Reviewer

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader

NDA: 20-933/20-636

Subject: Phase IV Commitments and Labeling Comments

Clinical request for Phase IV commitments

As a Phase IV commitment, we request that you specifically address the following issues in your complete study report of ACTG 245:

1. The efficacy of the double- and triple-regimen of nevirapine as measured by changes of surrogate markers over 48 weeks.

2. The appropriateness of a 2-week lead-in-dosing schedule as assessed by the incidence of rash events.

3. The characteristics of rash occurrence in children including the onset and accompanied symptoms and signs (such as allergic reactions)

4. The incidence of hepatic adverse events and the significance of the alkaline phosphatase level elevations in the study population.

Please provide your commitment in writing to the Division on Tuesday September 8, 1998.

Biopharmaceutical Comments on VIRAMUNE Package Insert

Please refer to the facsimile of the nevirapine label dated August 25, 1998. We recommend the following changes to the label.

1. Please refer to the section CLINICAL PHARMACOLOGY: Please add "See Precautions: Pediatric Use after "Pediatric Patients:"

2. Please move the pharmacokinetic information in pediatric patients to the section under Precautions: Pediatric Use, before the safety information.

3. Please delete the following lines: [redacted], and replace it with the following sentence: "The mean nevirapine apparent clearance adjusted for body weight was greater in children compared to adults".

4. Please delete the word [redacted] e "In a....(range 2 months-15 years)".

5. Please reword the sentence [redacted]" to read ""Nevirapine apparent clearance adjusted.....with increasing age".

6. Please reword the sentence " [redacted]" to read "Nevirapine apparent clearance adjusted for body weight was at least....compared to adults".

7. Please delete the following lines: [redacted]

8. Please note that since this information will be moved to the section under Precautions: Pediatric Use, the graph with nevirapine apparent clearance versus age would have a different figure number.

9. Please add the following sentence after the sentence "The relationship.....in Figure X": "The pediatric dosing regimens were selected in order to achieve steady-state plasma concentrations in pediatric patients that approximate those in adults. See Dosage and Administration".

10. For the graph titled "Nevirapine Apparent Clearance (ml/kg/hr) in Pediatric Patients", please plot only the first observable clearance in each patient versus age.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Kelly, MS, MBS, RN
Regulatory Health Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 20-933/20-636
Division File 20-933/20-636
HFD-530/CSO/Kelly
HFD-530/Chem/Lunn
HFD-530/MO/Wu
HFD-530/BP/Sekar

Facsimile

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 2, 1998

To: Clare Lavery
DRA Manager
Drug Regulatory Affairs

Address: Boehringer Ingelheim Pharmaceuticals, Inc.

From: Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer, HFD-530

Through: Dr. Teresa Wu, Medical Officer, HFD-530
Dr. Jeff Murray, Medical Team Leader, HFD-530

NDA: 20-636/SE1-009
20-933
(Reference [redacted]

SUBJECT: In preparation of a Written Request for pediatric information on VIRAMUNE (nevirapine), we would like to request from you the following information:

1. Please describe, in the original NDA submission, the content of the study report of Trial 1100.882 (ACTG 180). Was it a complete report including analyses of pk, surrogate markers, and safety? Or was it a report on safety only?

2. Please provide the age distribution of patients who enrolled into Trial 1100.1032 (ACTG 245) according to age groups, i.e., 1 month to 2 years, 2 to 12 years, 12 to 16 years, and 16 to 20 years.

3. Please provide us with a copy of the Executive Summary of Trial 1100.1032, if available. Please inform us whether this summary report includes the analyses of neurodevelopmental and neuropsychological data, if not, whether these analyses will be performed in the full report.

4. Please provide us your conservative estimates of the anticipated timeframes for the official submissions of study reports of ACTG 245 and PACTG 250 respectively.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/Wu
HFD-530/Lynche

cc:
Original NDA 20-636
Division File
HFD-530/Wu
HFD-530/Kelly

SAVE AS

APPEARS THIS WAY
ON ORIGINAL

530 -Kelly

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 20, 1998

To: Claire Lavery

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
Fax-203-791-6262

From: Teresa Wu, M.D., Ph.D., Medical Officer
Vanitha Sekar, Ph.D., Clinical Pharmacology and Biopharmaceutical Reviewer

/s/

NDA: 20-933/20-636

Subject: Labeling comments

Clinical Labeling comments on VIRAMUNE Pediatric PI

1. For Section: Pediatric **Patients,** we have the following comments:

In order to be consistent with the labeling format currently used by other approved antiretroviral drugs (e.g. Norvir and Viracept), we recommend that description of pediatric information be placed under the heading of ***Pediatric Use***, to be located immediately after the heading of ***Nursing Mothers*** in the package insert.

We also recommend the using following paragraph:

Safety has been assessed in an open-label trial BI 882 (ACTG180) (see CLINICAL PHARMACOLOGY, Pediatric Patients), in which 37 pediatric patients (age range 2 months to 15 years) were followed for a mean duration of 33.9 months (range 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 892). The most frequently reported adverse events related to VIRAMUNE in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children. In a double-blind, placebo-controlled trial of VIRAMUNE (ACTG 245, n=305) in which pediatric patients were received combination treatment with VIRAMUNE, two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome and three patients were reported to experience allergic reaction including one case of anaphylaxis. The evaluation of the antiviral activity of VIRAMUNE in pediatric patients in clinical trials is ongoing.

The safety and pharmacokinetic profile of VIRAMUNE in neonates has not been established.

2. For Table 4, we have the following comment:

   While the same criteria for various laboratory parameters are used to define 'marked laboratory abnormalities' in adults (Table 3) and children (Table 4), it should be pointed out that the ACTG grading criteria for hemoglobin and alkaline phosphatase differ slightly for these two populations. For example, hemoglobin < 8 g/dl is defined as Grade 3 or higher in adults but Grade 2 or higher in children of less than 2 years of age. We recommend that this difference be footnoted as appropriate in the labeling.

3. We recommend that the patient's instructions on how to administer the oral suspension be described in greater detail. For example, when administering volumes smaller than 5 ml, a dosing syringe should be used. Please comment on whether a graduated dosing spoon would be more convenient to use than a dosing cup. If you prefer a dosing cup, we ask that you conduct an experiment similar to the design of AS970024 in that the amount of drug product residue would be measured and demonstrated to be negligible after rinsing with water. We would like to know if any of the above measuring devices will be supplied in the same package with Nevirapine oral suspension.

Biopharmaceutical Comments

1. In reference to Figure 7.1, [redacted] the graph relating nevirapine apparent clearance (ml/kg/hr) and age). Please explain the following.

   A. How observed clearance values were calculated from single trough concentrations?

   B. What value(s) for body weight was used in the equation $TVCL=\theta_2+\theta_4*logBW$) to obtain the line representing typical values for nevirapine clearance.

2. In order to simplify review of the pharmacokinetic data from Study 1100.882, please submit the following information for each patient.

   A. Actual clearance values by treatment day (please indicate CL values calculated from trough measurements versus those from profiles).

   B. Trough concentrations and steady-state concentrations by treatment day (please indicate dosing history).

3. In reference to Figure 10.1, [redacted] ubmission number (298), Study 1100.882 (the graph showing nevirapine $C_{ss,avg}$ observed in adults and those predicted in children for various dosing regimens). Please submit a similar plot comparing actual nevirapine $C_{ss,avg}$ observed in pediatric patients in 1100.882 for the four different dosing regimens

Please respond to FDA prior to August 26, 1998, at which time we have scheduled a tentative teleconference with the Division, if further discussion or clarification is needed.

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Christine Kelly, MS, MBS, RN
Regulatory Health Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-933/20-636
Division File 20-933/20-636
HFD-530/CSO/Kelly
HFD-530/Chem/Lunn
HFD-530/MO/Wu
HFD-530/BP/Sekar

Facsimile

MESSAGE CONFIRMATION

08/20/98 14:13
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173	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 20, 1998

To: Claire Lavery

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
Fax-203-791-6262

From: Teresa Wu, M.D., Ph.D., Medical Officer
Vanitha Sekar, Ph.D., Clinical Pharmacology and Biopharmaceutical Reviewer

NDA: 20-933/20-636

Subject: Labeling comments

Clinical Labeling comments on VIRAMUNE Pediatric PI

1. For Section: Pediatric **Patients,** we have the following comments:

   In order to be consistent with the labeling format currently used by other approved antiretroviral drugs (e.g. Norvir and Viracept), we recommend that description of pediatric information be placed under the heading of ***Pediatric Use***, to be located immediately after the heading of ***Nursing Mothers*** in the package insert.

   We also recommend the using following paragraph:

   Safety has been assessed in an open-label trial BI 882 (ACTG180) (see CLINICAL PHARMACOLOGY, Pediatric Patients), in which 27 pediatric patients (age range 2 months to

530 Kelly

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 19, 1998

To: Claire Lavery

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
Fax-203-791-6262

From: George Lunn, Ph.D., Chemistry Reviewer, HFD-530

Through: Steve Miller, Chemistry Team Leader, HFD-530 CK for SM

NDA: 20-933/20-636

Subject: Chemistry comments on stability testing

Chemistry Comments -

In your commitment for the stability testing of commercial batches of drug substance (volume 3, p. 279) you state that the drug substance will be monitored for the following:

Visual Appearance
Identity by [redacted]
[redacted] for Impurities
Particle Size by [redacted]
Water by [redacted]

This does not appear to include an assay for nevirapine. Is this correct or was the requirement for a nevirapine assay inadvertently omitted?

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/S/

Christine Kelly, MS, MBS, RN
Regulatory Health Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 20-933/20-636
Division File 20-933/20-636
HFD-530/CSO/Kelly
HFD-530/Chem/Lunn

Facsimile

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

530 Kelly

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 6, 1998

To: Claire Lavery

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
Fax (203) 791-6262

From: Teresa Wu, M.D., Ph.D., Medical Officer, DAVDP

Through: Sam Maldonado, M.D., M.P.H., Acting Team Leader, DAVDP

/S/

NDA: 20-933/20-636 (SE1-009)

Subject: **Labeling comments pertaining to the nevirapine suspension NDA and nevirapine pediatric supplement.**

In response to your Amendment no. 2 to NDA 20-636 supplement (06/12/98), we are providing in this correspondence the clinical comments on the proposed package insert for VIRAMUNE tablets and oral suspension. Comments on pk and chemistry of the oral suspension will be provided at a later date. We ask that your labeling revision be received by us no later than August 14, 1998.

1. Section: *Pediatric Patients*

For this section, please use exclusively the data derived from trial 1100.882 to provide a text description of sample size, age range, dosing regimen, duration of exposure , and tabulations of the incidence of NVP-related adverse events, and percentage of pediatric patients with marked laboratory abnormalities.

Due to the fact that only a fraction of patients from trial 1100.882 enrolled in trial 1100.892 (long-term treatment up to 5.3 years) and that there were no activity data of NVP provided for trial 1100.892, we feel that to present the safety information of NVP by combining results of trial 1100.882 and trial 1100.892 might potentially mislead the prescribing physician to interpret that durability of the efficacy activity of NVP based on surrogate markers were established in clinical studies.

Since results of ACTG 245 have not been fully analyzed, there should be no mention in this section on the sample size, demographics or duration of exposure of the trial. We suggest that you refer ACTG 245 in the labeling as: A comparative study of combination antiretroviral therapy including NVP in children and aldolescents with HIV disease has completed but data have not been fully analyzed. In that study, there were reports of two cases of SJS and three cases of allergic reactions including anaphylaxis.....

2. Section **DOSAGE AND ADMINISTRATION:** ***Pediatric Patients***

Please provide a detailed instruction on method(s) of administration to ensure the consumption of the full dose of the suspension. Please submit any actual use data to support your statement.

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/S/

Christine Kelly, MS, MBA, RN
Regulatory Health Project Manager
Division of Antiviral Drug Products

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DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 443-9550 • Fax: (301) 443-9292

Concurrence:
HFD-530/AMTL/M. /S/
HFD-530/MO/Wu /S/
HFD-530/CSO/Kelly

cc:
Original NDA 20-933
Division File 20-933/20-636
HFD-530/CSO/Kelly
HFD-530/MO/Wu

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MESSAGE CONFIRMATION

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06/98 16:36 DAVDP → 912037916262 NO.754 D01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Claire Lavery

FAX Number: (203) 791-6262

Date: August 6, 1998

Company: Boehringer Ingelheim

Address:

No. pages (excluding cover): 2

Message:

530 - Kelly

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 24, 1998

To: Clare Lavery
DRA Manager
Drug Regulatory Affairs

Address: Boehringer Ingelheim Pharmaceuticals, Inc.

From: Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer, HFD-530

Through: Dr. Teresa Wu
Medical Team Leader, HFD-530

NDA: 20-636

SUBJECT: Clarification regarding NDA 20-636

1. Please provide or locate the original versions of protocols for Trial 882, 892 and 1032 (not clinical synopsis).

2. Tables 2372:2 and 2374:1 (vol. 37.2): Please explain how incidences of rash in the monotherapy group were calculated. Please explain why the 6 patients who experienced adverse events during an interruption in ZDV dosing were excluded for the calculation of rash incidence but not for other adverse events.

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/S/

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

Concurrence:
HFD-530/Wu
HFD-530/Lynche /S/ 7/24/98

cc:
Original NDA 20-636
Division File
HFD-530/Wu
HFD-530/Kelly

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MESSAGE CONFIRMATION

08/23/98 13:51

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/23	00'49"	203 791 6262	CALLING	02	OK	0000

08/23/98 13:49 NO.085 D01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Clare Lavery, Drug Regulatory Affairs

Fax Number: (203) 791-6262

Date: July 24, 1998

Company: Boehringer Ingelheim Pharmaceuticals, Inc.

No. of pages (excluding cover): 1

Message: Clarification regarding NDA 20-636

HFD-530/CSO/Kelly

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 09,1998

To: Pamela Strode

Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

From: George Lunn, Chemistry Reviewer, HFD-530

Through: Steve Miller, Chemistry Team Leader, HFD-530 SM

NDA: 20-933

Subject: Chemistry comments pertaining to the nevirapine suspension NDA.

Chemistry Comments - Please address the following items.

1. Please provide a justification for the Microbial Limits specification for the Drug Substance. In particular, please consider revising the total microbial count specification of [redacted] cfu/g in view of the test results of [redacted] (volume 3, pp. 263-266).

2. We recommend that pH be included as a regulatory specification that the product would meet throughout its shelf life. There were some pH failures but only after 12 months at 40°C/75% RH, which are very severe conditions. We would therefore recommend that pH be included in the commercial stability protocol. If desired, a tighter in-house specification for "pH at release" may also be established.

3. In the NDA a provisional shelf-life of [redacted] is proposed (Volume 5, p. 5 72). On the basis of 6 months stability data for the recapped primary stability batches and 12 months stability data for the non-recapped batches we recommend a shelf-life of [redacted] Although supportive stability data out to [redacted] are presented on batches PD 1237 and PD 1313, the formulation for these batches differs in that the Carbomer 934P concentration is [redacted] However, if satisfactory stability data obtained at 12 months for the recapped batches and 18 months for the non-recapped batches are submitted to the NDA before August 1, 1998 a shelf life of [redacted] could be recommended at the time of approval.

4. Please refer to point 14 of the FDA minutes of the FDA meeting with Boehringer Ingelheim on July 10, 1997 for discussion of uniformity issues.

   a. We understand that [redacted] is proposed in the NDA as an [redacted] (Volume 4, p. 271). However, it is not clear how this would work. How would this procedure guard against, for example, inadvertent dilution of the product with water trapped in the transfer lines? (Water in the transfer lines was proposed to explain some of the anomalous stability results.) What is the density of the suspension? How much water would need to be introduced before the weight of the bottle exceeded the specification (assuming a worst case scenario)?

   b. We are interested in two aspects of concentration uniformity: within an individual container and across a production run. Intra-bottle uniformity is controlled by analyzing multiple samples from the same bottle and primarily addresses settling issues. We agree that this control should be applied to the first 3 [redacted] batches at release and, if the data warrant, then be discontinued.

   c. Inter-bottle uniformity, i.e., assaying sample bottles for nevirapine throughout the production run, does not appear to be satisfactorily addressed. In view of the problems with accidental dilution of the suspension we would like to see an inter-container dose uniformity control using an [redacted] This could either be an in-process control or a regulatory specification.

   d. Please summarize the data that show that a uniform suspension is achieved by gentle shaking prior to dispensing. Are any instructions to the patient necessary to insure uniformity of dosing under "in-use" conditions?

5. Please describe the calibration procedure for the Particle Size Analysis. While we realize that you have performed ruggedness testing and shown that the results are reproducible it is not clear how the absolute accuracy is established. Has long term drift in the calibration been found to be a problem?

6. Please clarify the compositions of Working Standard #1 and Working Standard #2 (Volume 4, p. 245) and Impurity Standard #1 and Impurity Standard #2 (Volume 4, p. 255).

7. On p. 181 of volume 2 [redacted] Please correct this apparent typographical error.

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/S/

Christine Kelly, MS, MBS, RN
Regulatory Health Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 20-933
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HFD-530/CSO/Kelly
HFD-530/Chem/Lunn

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