

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-785**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

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.	
<b>PATENT INFORMATION SUBMITTED WITH THE          FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and          Composition) and/or Method of Use</i>		NDA NUMBER 21-785	
		NAME OF APPLICANT / NDA HOLDER <b>Hoffmann-La Roche Inc.</b>	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) <b>Invirase</b>			
ACTIVE INGREDIENT(S) <b>Saquinavir Mesylate</b>		STRENGTH(S) <b>500mg</b>	
DOSAGE FORM <b>Film Coated Tablet</b>			
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 <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> 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.			
<b>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.</b>			
<b>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.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number <b>5,196,438</b>		b. Issue Date of Patent <b>March 23, 1993</b>	c. Expiration Date of Patent <b>November 19, 2010</b>
d. Name of Patent Owner  <b>HLR Technology Corporation</b>		Address (of Patent Owner) <b>340 Kingsland Street</b>	
		City/State <b>Nutley, New Jersey</b>	
		ZIP Code <b>07110</b>	FAX Number (if available) <b>(973) 235-2363</b>
		Telephone Number <b>(973) 235-4391</b>	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.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

<b>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.</b>		
<b>2. Drug Substance (Active Ingredient)</b>		
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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<b>3. Drug Product (Composition/Formulation)</b>		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<b>4. Method of Use</b>		
<b>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:</b>		
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?		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	
15	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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.)  "INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV infection."	
<b>5. No Relevant Patents</b>		
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.		<input type="checkbox"/> 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.**

<p><b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b></p> <p><i>Eileen M. Ebel</i></p>	<p>Date Signed</p> <p>5/28/04</p>
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**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.

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name <b>Eileen M. Ebel</b>	
Address <b>340 Kingsland Street</b>	City/State <b>Nutley, New Jersey</b>
ZIP Code <b>07110</b>	Telephone Number <b>(973) 235-4391</b>
FAX Number (if available) <b>(973) 235-2363</b>	E-Mail Address (if available)

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.*

EXCLUSIVITY SUMMARY FOR NDA # 21-785 SUPPL #N/A

Trade Name Invirase<sup>®</sup> Generic Name Saquinavir Mesylate

Applicant Name Hoffman-La Roche Inc. HFD # 530

Approval Date If Known December 17, 2004

**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 question about the submission.

a) Is it a 505(b) (1), 505(b) (2) or efficacy supplement?  
YES /X/ NO /  /

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

**505 (b) (1)**

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.

**The NDA contains the results of three studies to show the relative bioavailability and bioequivalence of the Invirase 200 mg hard gel capsules to the Invirase 500 mg film coated tablets.**

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 /X/

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

\_\_\_\_\_

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

YES /\_\_\_/ NO /X/

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?

\_\_\_\_\_

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 /X/

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 / X / NO / \_\_\_ /

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

NDA# 20-628 Invirase capsule \_\_\_\_\_

NDA# 20-828 Fortovase \_\_\_\_\_

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 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 /X/

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:

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(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:

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(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:

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(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:

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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



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"):

\_\_\_\_\_  
\_\_\_\_\_

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 \_\_\_\_\_  
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/s/

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Debra Birnkrant  
12/17/04 04:30:04 PM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-785 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: June 18, 2004 Action Date: December 17, 2004

HFD 530 Trade and generic names/dosage form: Invirase® (saquinavir mesylate) 500 mg Film Coated Tablet

Applicant: Hoffman-La Roche Therapeutic Class: Antiviral

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: Invirase in combination with other antiretroviral agents is indicated for the treatment of HIV infection in adults.

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:

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 4 yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. 0 yr. 18 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: Hoffman-La Roche has initiated a development program for pediatric patients that is currently ongoing. Written request most recently amended on November 10, 2004

Date studies are due (mm/dd/yy): March 31, 2006

*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:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ 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.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-785  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

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/s/

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Kenny Shade  
12/17/04 02:36:41 PM

**INVIRASE®** (saquinavir mesylate)  
500 mg tablet



4  
Administrative documents  
Module 1 Volume 1

## **DEBARMENT CERTIFICATION**

**Hoffmann-La Roche 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.**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

**Date:** December 7, 2004

**To:** Matthew Lamb, Pharm.D.  
Associate Director  
Global Regulatory Affairs  
Hoffman-La Roche  
340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Kenny Shade, JD, BSN, Regulatory Project Manager, HFD-530

**Through:** Narayana Battula, Ph.D., Microbiology Reviewer

**Concurrence:** Julian O'Rear, Ph.D., Microbiology Team Leader

**Subject:** NDA 21-785 [Invirase® (saquinavir mesylate) 500 mg]

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The following information request is made on behalf of Dr. Narayana Battula:

- Please submit the *in vitro* antiviral activity of saquinavir against HIV-2.  
(Your letter of November 2, 2004 to DAVDP stated that this report should be available by the end of November 2004).
- Please submit a report of the *in vitro* combination activity relationships of saquinavir with all approved antiretroviral drugs not currently covered in the label.  
(This is a phase IV Commitment, item #8, made with the approval of supplemental NDAs for Fortovase and Invirase on December 24, 2003).

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

---

Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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Kenny Shade  
12/7/04 09:54:20 AM  
CSO

This is the microbiology team information request.

Kathrine Laessig  
12/7/04 03:51:12 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

**Date:** December 3, 2004

**To:** Matthew Lamb, Pharm.D.  
Associate Director  
Global Regulatory Affairs  
Hoffman-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Kenny Shade, JD, BSN, Regulatory Project Manager, HFD-530

**Through:** Yoshihiko Murata, M.D., Ph.D., Medical Officer  
Narayana Battula, Ph.D., Microbiology Reviewer

**Concurrence:** Katherine Laessig, M.D., Medical Officer Team Leader  
Julian O'Rear, Ph.D., Microbiology Team Leader

**Subject:** NDA 21-785 [Invirase® (saquinavir mesylate) 500 mg]  
Proposed Post-Marketing Commitments (PMCs) and  
Request for Clarification of Information for the Proposed Package Insert

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Please refer to your June 17, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invirase® (saquinavir mesylate) 500 mg film coated tablet.

Please note the following proposed Post Marketing Commitments from the review team for NDA 21-785 [Invirase® (saquinavir mesylate) 500 mg film coated tablet]. Additionally, please note the request for clarification regarding the MaxCmin 1 study demographics as shown on the proposed package insert.

**Clinical Proposed Post-Marketing Commitments:**

1. Conduct a retrospective analysis on the effects of gender on the safety profile of SQV 1000 mg/RTV 100 mg. Safety data should be provided from at least 50-100 female participants with appropriately matched comparative data from male subjects.

Timeline: Final study report due twelve months from action date.

2. Conduct a safety analysis by gender and saquinavir levels for subjects who received SQV 1000 mg/RTV 100 mg and were enrolled in the pharmacokinetic substudies of the MaxCmin 1 and MaxCmin 2 studies. Data from the two studies should be pooled for analysis and a uniform adverse event coding system should be used.

Timeline: Final study report due twelve months from action date.

**Microbiology Proposed Post-Marketing Commitments:**

3. Determine the baseline genotype of all PI-experienced responders in the MaxCmin 1 and MaxCmin 2 studies and submit in the resistance template format. Resubmit MaxCmin 1 and MaxCmin 2 failure dataset with a column identifying isolate (specifically "baseline") and with a column identifying outcome (nonresponder, rebound, censored, etc.).

Timeline: Final study report due six months from action date.

**Request for Clarification for the Proposed Package Insert (p. 9, Description of Clinical Studies):**

In the MaxCmin 1 study, please clarify the number of subjects who received SQV/RTV and were treatment-naïve or treatment-experienced at the start of the study. The proposed Package Insert states that at baseline, 42 subjects were treatment-naïve. Based on our analysis, 68 (16 females, 52 males) out of 148 subjects were treatment-naïve. Our results were based on the medication history of patients prior to the variable 'basedate' and using the datasets DEMO.XPT and MEDO.XPT.

Please respond to proposed post-marketing commitments and request for clarification for the proposed package insert by COB 12/8/04.

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

---

Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Kenny Shade  
12/6/04 08:31:50 AM  
CSO

Proposed PMCs for NDA 21-785 (Invirase 500mg FTC)

Kathrine Laessig  
12/6/04 09:30:54 AM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

**Date:** November 30, 2004

**To:** Matthew Lamb, Pharm.D.  
Senior Program Manager  
Drug Regulatory Affairs  
Hoffman-La Roche  
340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Kenny Shade, JD, BSN, Regulatory Project Manager, HFD-530

**Through:** Lorenzo Rocca, Ph.D.

**Subject:** NDA 21-785 [Invirase® (saquinavir mesylate) 500 mg]

The following information request is made on behalf of Dr. Lorenzo Rocca:

- The sponsor states that the release specifications for INVIRASE® (saquinavir mesylate) Film Coated Tablet, 500 mg reflect the sponsor's analytical experience obtained during the development of INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablet, 500 mg. In light of this statement please provide the FDA with justification for not including moisture and microbiological control testing for INVIRASE® (saquinavir mesylate) Film Coated Tablet, 500 mg.

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Kenny Shade, JD,  
Regulatory Project Manager  
Division of Antiviral Drug Products  
HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Kenny Shade  
11/30/04 01:12:35 PM  
CSO

CMC comment

Stephen Paul Miller  
12/6/04 09:02:39 AM  
CHEMIST



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-785  
**Drug:** Invirase 500mg FCT  
**Date:** October 15, 2004  
**To:** Matthew Lamb, Pharm.D.  
**Sponsor:** Hoffman-La Roche  
**From:** Kenny Shade, JD, BSN  
**Through:** K. M. Wu, PhD, Pharmacology/Toxicology Reviewer  
**Concur:** Katherine Laessig, MD, Medical Team Leader  
James Farrelly, PhD, Pharmacology/Toxicology Team Leader  
**Subject:** Pharmacology/Toxicology Comment

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA 21-785) for Invirase FTC.

**Pharmacology/Toxicology Comments**

along

- 1) Please submit in tabular format the AUC information from animal reproductive studies with the human study that will be served as the reference for drug exposure comparison. Example of format can be as follows:

Reproductive Toxicity Studies	Dose (mg/kg/day)	AUC (units)	Ratio (Human/Animal)
Rat			
Rabbit			
Reference Human Study (proposed by the sponsor)			

August 11, 2004

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Kenny Shade  
10/15/04 02:28:35 PM  
CSO

Kathrine Laessig  
10/19/04 04:11:12 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

**Date:** September 23, 2004

**To:** Matthew Lamb, Pharm.D.  
Senior Program Manager  
Drug Regulatory Affairs  
Hoffman-La Roche  
340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Kenny Shade, JD,BSN, Regulatory Project Manager, HFD-530

**Through:** Jen DiGiacinto, Pharm.D.

**Subject:** NDA 21-785 [Invirase® (saquinavir mesylate) 500 mg]

---

The following request is made on behalf of Dr. Jen DiGiacinto:

- 1) Please provide the actual specification for your selected method (i.e. Q = what?).
- 2) Please provide the individual dissolution data from both clinical and commercial batches.
- 3) Please provide the number of tablets that was used in each dissolution study.
- 4) Please provide detail information about the analytical method used in the dissolution studies.

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Kenny Shade  
9/23/04 11:32:02 AM  
CSO



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-785  
**Drug:** INVIRASE® (Saquinavir Mesylate)  
**Date:** August 31, 2004  
**To:** Matthew Lamb, Pharm.D.  
**Sponsor:** Hoffman-La Roche  
**From:** Kenny Shade, JD, BSN  
**Through:** Kuei-Meng Wu, Ph.D., Pharm. Tox. Reviewer  
**Concur:** Katherine Laessig, MD, Medical Team Leader  
James Farrelly, Ph.D., Pharmacologist, Team Leader, Associate Director  
**Subject:** Pharmacologist Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA 21-785) for Invirase (Saquinavir Mesylate) 500 mg.

**Pharmacologist**

- Please submit in tabular format the AUC information from carcinogenicity studies along with those in humans at the clinical recommended doses, in support of Pharm/Tox labeling proposal in NDA 21-785. Example of format can be as follows:

**Saquinavir Exposures (AUC) Comparisons**

Carcinogenicity Study	Sex	Dose (mg/kg/day)	AUC (units)	Ratio (Human/Animal)
Rat	M			
	M			
	M			
	F			
	F			
	F			
Mice	M			
	M			
	M			
	F			

August 31, 2004

	F			
	F			
Human Study No.				

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Kenny Shade  
8/31/04 01:29:53 PM  
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NDA 21-785 (Invirase 500mg FCT)

Kathrine Laessig  
8/31/04 01:37:36 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-785

Hoffman-La Roche  
Attention: Matthew Lamb, Pharm.D.  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Lamb:

Please refer to your June 17, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invirase® (saquinavir mesylate) 500 mg film coated tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 16, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues; however, we request that the following information be provided to the Division.

**CLINICAL**

- Please provide all datasets from the MaxCmin 1 study that were used for the safety analysis for this NDA. The AEs in these datasets have been re-coded using MeDRA. The safety datasets are to contain AEs from all subjects who took SQV/RTV as well as those (n = 69) who underwent pharmacokinetics monitoring at week 4.
- Please provide all SAS programs that were used to analyze the MaxCmin 1 dataset for the Invirase® 500 mg tablets NDA.
- Please provide the MaxCmin 1 PK data (as shown in Module 5, Volume 16, p. 15) in electronic format.

**CLINICAL PHARMACOLOGY**

- Please submit the complete Dissolution Study Report that contains the method justification, data indicating the discriminatory power of the method, and individual tablet data, as requested at the pre-NDA teleconference (dissolution report to be included in the Common Technical Document Summaries Module 2 section).

**MICROBIOLOGY**

- Please submit the MaxCmin 1 and MaxCmin 2 resistance study report (postmarketing commitment due July, 2004) and datasets in the HIV resistance template format.
- Please submit a draft report of the *in vitro* combination activity relationships of saquinavir with all approved antiretroviral drugs not currently covered in the label (postmarketing commitment due September, 2004).
- Please provide *in vitro* antiviral activity data for multiple isolates of the different HIV clades and for HIV-2.

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.

If you have any questions, call Kenny Shade, J.D., B.S.N., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Jeffrey Murray  
8/17/04 04:44:49 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

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

**45-DAY FILING MEETING MINUTES**

**NDAs:** 21-785

**DATE:** July 27, 2004

**DRUG:** Invirase (saquinavir mesylate) 500 mg film coated tablet

**APPLICANT:** Hoffman-La Roche

<b>PARTICIPANTS:</b>	<b>Debra Birnkrant, M.D.</b>	<b>Division Director</b>
	<b>Katherine Laessig, M.D.</b>	<b>Medical Team Leader</b>
	<b>Yoshihiko Murata, M.D., Ph.D.</b>	<b>Medical Reviewer</b>
	<b>Kuei-Meng Wu, Ph.D.</b>	<b>Pharmacology/Toxicology Reviewer</b>
	<b>Lorenzo Rocca, Ph.D.</b>	<b>Chemistry Reviewer</b>
	<b>Jules O'Rear, Ph.D.</b>	<b>Microbiology Team Leader</b>
	<b>Narayana Battula, Ph.D.</b>	<b>Microbiology Reviewer</b>
	<b>Greg Soon, Ph.D.</b>	<b>Statistics Team Leader</b>
	<b>Susan Zhou, Ph.D.</b>	<b>Statistics Reviewer</b>
	<b>Kellie Reynolds, Pharm.D.</b>	<b>Biopharmaceutics Team Leader</b>
	<b>Jennifer DiGiacinto, Pharm.D.</b>	<b>Biopharmaceutics Reviewer</b>
	<b>Kenny Shade, J.D., B.S.N.</b>	<b>Regulatory Project Manager</b>
	<b>Virginia Behr</b>	<b>Chief, Regulatory Project Management Staff</b>
	<b>Kim Bergman</b>	<b>Clinical Pharmacologist</b>
	<b>Adam Shprecher, Pharm.D.</b>	<b>Pharm.D. Fellow</b>
	<b>Bonnie Brennen, Pharm.D.</b>	<b>Pharm.D. Fellow</b>

**BACKGROUND:**

Hoffman-La Roche submitted this new drug application for an additional saquinavir mesylate formulation for use in the treatment of HIV-1 infected patients.

This NDA was submitted on June 17, 2004 and was received on June 18, 2004. Hoffman-La Roche has submitted this NDA in the electronic common technical document (CTD) format and paper.

**CHEMISTRY (CMC):**

This submission is fileable from the CMC perspective. There are no comments to convey at this time.

## **PHARMACOLOGY/TOXICOLOGY:**

This submission is fileable from the Pharm/Tox perspective. There are no comments to convey at this time.

## **MICROBIOLOGY:**

This submission is fileable from the Microbiology perspective. However, the following comments will be conveyed to the sponsor in a fax and the 74-day letter.

- Please submit for review the MaxCmin 1 and MaxCmin 2 resistance study report (Phase 4 commitment due July, 2004) and datasets in the HIV resistance template format (attached).
- Please submit a draft report of the *in vitro* combination activity relationships of saquinavir with all approved antiretroviral drugs not currently covered in the label (Phase 4 commitment due September, 2004).
- Please provide *in vitro* antiviral activity data for multiple isolates of the different HIV clades and for HIV-2.

## **CLINICAL PHARMACOLOGY:**

This submission is fileable from the Biopharmaceutics perspective. However, the following comment will be conveyed to the sponsor in a fax and the 74-day letter.

- Please submit the complete Dissolution Study Report that contains the method justification, data indicating the discriminatory power of the method, and individual tablet data, as requested at the pre-NDA teleconference (dissolution report to be included in the Common Technical Document Summaries Module 2 section).

## **CLINICAL:**

This submission is fileable from the Clinical perspective. However, the following comment will be conveyed to the sponsor in a fax and the 74-day letter.

- Please submit all datasets from the MaxCmin 1 study that were used for the safety analysis for this NDA. The AEs in these datasets have been re-coded using MedDRA. The safety datasets are to contain AEs from all subjects who took SQV/RTV as well as those (n = 69) who underwent PK monitoring at week 4.
- Please submit all SAS programs that were used to analyze the MaxCmin 1 data set for the INVIRASE® 500 mg tablets NDA.
- Please submit the MaxCmin 1 PK data (as shown in Module 5, Volume 16, p. 15) in electronic format.

**STATISTICS:**

This submission is fileable from the statistical perspective. There are no comments to convey at this time.

**ADVISORY COMMITTEE MEETING**

The Division determined that an advisory committee meeting is not necessary.

**Division of Scientific Investigations (DSI)**

The Division of Scientific Investigations notified of new NDA, but no inspection specifically requested.

**CONCLUSION/ACTION ITEMS:**

- This application is fileable and will be granted a priority review.
- The microbiology, clinical pharmacology and clinical comments will be sent to the sponsor in a fax and the 74-day letter.
- The PDUFA date is December 18, 2004.

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/s/

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Kathrine Laessig  
8/16/04 01:48:05 PM



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-785  
**Drug:** INVIRASE® (Saquinavir Mesylate)  
**Date:** August 12, 2004  
**To:** Matthew Lamb, Pharm.D.  
**Sponsor:** Hoffman-La Roche  
**From:** Kenny Shade, JD, BSN  
**Through:** Jennifer DiGiacinto, Pharm.D.  
Narayana Battula, PhD  
**Concur:** Katherine Laessig, MD, Medical Team Leader  
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader  
Yoshihiko Murata, MD, PhD, Medical Reviewer  
Julian O'Rear, PhD, Microbiology Team Leader  
**Subject:** Clinical Pharmacology and Microbiology Comments

---

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA 21-785) for Invirase (Saquinavir Mesylate) 500 mg.

**Clinical Pharmacology**

- Please submit the complete Dissolution Study Report that contains the method justification, data indicating the discriminatory power of the method, and individual tablet data, as requested at the pre-NDA teleconference (dissolution report to be included in the Common Technical Document Summaries Module 2 section).

**Microbiology**

- Please submit for review the MaxCmin 1 and MaxCmin 2 resistance study report (Phase 4 commitment due July, 2004) and datasets in the HIV resistance template format.
- Please submit a draft report of the *in vitro* combination activity relationships of saquinavir with all approved drugs not currently covered in the label (Phase 4 commitment due September, 2004).
- Please provide *in vitro* antiviral activity data for multiple isolates of the different HIV clades and for HIV-2.

August 11, 2004

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Kenny Shade  
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CSO

Kathrine Laessig  
8/12/04 11:24:37 AM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-785

**Drug:** INVIRASE® (Saquinavir Mesylate)

**Date:** July 28, 2004

**To:** Matthew Lamb, Pharm.D.

**Sponsor:** Hoffman-La Roche, Inc.

**From:** Kenny Shade, JD, BSN                      **Regulatory Project Manager**

**Through:** Yoshihiko Murata, MD, PhD              **Medical Reviewer**

**Concur:** Katherine Laessig, M.D.                      **Medical Team Leader**

**Subject:** NDA 21-785 Teleconference Discussion

---

Please refer to your new drug application (NDA 21-785) for Invirase (Saquinavir Mesylate) 500 mg.

As discussed in a teleconference on July 28, 2004 between Roche representatives (including Drs. Matthew Lamb and Wendy Snowden) and FDA representatives Dr. Yoshihiko Murata and Kenny Shade, it is our understanding that the following items are currently available for the Division's review of INVIRASE® 500 mg tablet NDA:

1. All datasets from the MaxCmin 1 study that were used for the safety analysis for this NDA. The AEs in these datasets have been re-coded using MeDRA. The safety datasets are to contain AEs from all subjects who took SQV/RTV as well as those (n = 69) who underwent PK monitoring at week 4.
2. All SAS programs that were used to analyze the MaxCmin 1 dataset for the INVIRASE® 500 mg tablets NDA.
3. The MaxCmin 1 PK data (as shown in Module 5, Volume 16, p. 15) in electronic format.

It is our understanding that all of these items are to be expedited to the Division.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-827-2335.

NDA 21-511  
March 29, 2004

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Kenny Shade  
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CSO

Kathrine Laessig  
7/29/04 03:57:59 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-785

Hoffman-La Roche Inc.  
Attention: Matthew Lamb, Pharm.D.  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Lamb:

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: Invirase (saquinavir mesylate) 500mg film-coated tablet for oral administration

Review Priority Classification: Priority

Date of Application: June 17, 2004

Date of Receipt: June 18, 2004

Our Reference Number: NDA 21-785

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 August 16, 2004 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be December 18, 2004.

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 requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

NDA21-785

Page 2

Center for Drug Evaluation and Research  
Division of Antiviral Drug Products, HFD-530  
Attention: Document Control Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Drug Products, HFD-530  
Attention: Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, MD, Division Director  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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