



WRITTEN REQUEST – AMENDMENT #5

NDA 20-628
NDA 21-785
IND 41,099

Hoffman-La Roche
Attention: Barbara Taylor
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Taylor:

Please refer to your correspondence dated August 30, 2007, requesting changes to FDA's April 9, 1999 Written Request for pediatric studies for saquinavir mesylate.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on April 9, 1999, as amended December 20, 2001, November 10, 2004, and February 23, 2007, remain the same.

The section, Type of Studies, has been amended to substitute "saquinavir or saquinavir mesylate" for "saquinavir mesylate":

Type of studies:

Multiple-dose pharmacokinetic, safety and activity study (ies) of **saquinavir or saquinavir mesylate** boosted with low-dose Ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic, safety and activity study (ies) of **saquinavir or saquinavir mesylate** boosted with lopinavir/Ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

The objective of these studies will be to determine the pharmacokinetic and safety profile of **saquinavir or saquinavir mesylate** boosted with ritonavir or lopinavir/ritonavir across the age range studied, identify and appropriate dose of INVIRASE® (saquinavir mesylate) for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

The Drug Information section has been amended to include all formulations of saquinavir or saquinavir mesylate that have been used in clinical trials:

Drug Information:

Dosage forms:

- Saquinavir mesylate 200 mg hard gelatin capsules (INVIRASE®)
- Saquinavir mesylate 500 mg film-coated tablets (INVIRASE®)

- **Saquinavir (Fortovase®) 200 mg soft-gel capsule [Note: Fortovase® is no longer commercially available.]**
- Age appropriate-formulation

The Drug-specific safety concerns section has been amended to substitute substitute “saquinavir or saquinavir mesylate” for “saquinavir mesylate”:

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including the following:

- Tolerance of capsule size and palatability
- Gastrointestinal adverse events
- Increases in hepatic transaminases and bilirubin
- Metabolic disorders such as hyperglycemia and hyperlipidemia, and abnormal fat redistribution.

Safety of saquinavir or saquinavir mesylate must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range.

Study Endpoints:

The Study Endpoints “Safety and Tolerability” section has been amended to all forms of saquinavir or saquinavir mesylate that have been used in clinical trials. Additionally, the Study Endpoints “Resistance” section has been amended to allow either genotypic or phenotypic testing of clinical isolates:

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max} , C_{min} , T_{max} , $t_{1/2}$, AUC and apparent oral clearance.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. In addition, please also submit plans for long-term safety monitoring in HIV infected pediatric patients who have received saquinavir or saquinavir mesylate. Safety data must be collected on at least 75 patients.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving saquinavir or saquinavir mesylate, particularly from those who experience loss of virologic response.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated April 9, 1999, as amended by this letter and by previous amendment(s) dated December 20, 2001, November 10, 2004, and April 23, 2007, must be submitted to the Agency on or before **August 1, 2010**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that saquinavir mesylate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-796-0807.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment (Complete Copy of Written Request as amended)



NDA 20-628
NDA 21-785
IND 41,099

WRITTEN REQUEST - AMENDMENT

Hoffman-La Roche
Attention: Barbara Taylor
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Taylor:

Reference is made to your Pediatric Written Request for saquinavir to IND 41,099 issued April 9, 1999, as amended December 20, 2001, November 10, 2004, and February 23, 2007. Reference is also made to your August 30, 2007 submission.

To obtain needed pediatric information on INVIRASE® (saquinavir mesylate), the Food and Drug Administration (FDA) is hereby making another formal Written Request, pursuant to Section 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies. This Written Request supersedes all earlier versions.

Type of studies:

Multiple-dose pharmacokinetic, safety and activity study (ies) of saquinavir or saquinavir mesylate boosted with low-dose ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic, safety and activity study (ies) of saquinavir or saquinavir mesylate boosted with lopinavir/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

The objective of these studies will be to determine the pharmacokinetic and safety profile of saquinavir or saquinavir mesylate boosted with ritonavir or lopinavir/ritonavir across the age range studied, identify and appropriate dose of INVIRASE® (saquinavir mesylate) for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

Indication to be studied:

Treatment of HIV infection in pediatric patients in combination with other antiretroviral agents.

Age group in which studies will be performed:

HIV-infected pediatric patients from 4 months to 16 years of age.

Drug Information:

Dosage forms:

- Saquinavir mesylate 200 mg hard gelatin capsules (INVIRASE®)
- Saquinavir mesylate 500 mg film-coated tablets (INVIRASE®)
- Saquinavir (Fortovase®) 200 mg soft-gel capsule [Note: Fortovase® is no longer

- commercially available.]
- Age appropriate-formulation

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the study (ies) described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults. Any studies supporting the use of a proposed compounded formulation (palatability, bioavailability) should be submitted before or with the pediatric supplement.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including the following:

- Tolerance of capsule size and palatability
- Gastrointestinal adverse events
- Increases in hepatic transaminases and bilirubin
- Metabolic disorders such as hyperglycemia and hyperlipidemia, and abnormal fat redistribution.

Safety of saquinavir or saquinavir mesylate must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers). A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic study(ies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

- 4 months to < 2 years: 8
- 2 years to < 6 years: 12
- 6 years to < 12 years: 8
- 12 years to < 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be generally well distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max} , C_{min} , T_{max} , $t_{1/2}$, AUC and apparent oral clearance.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. In addition, please also submit plans for long-term safety monitoring in HIV infected pediatric patients who have received saquinavir or saquinavir mesylate.

Safety data must be collected on at least 75 patients.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving saquinavir or saquinavir mesylate, particularly from those who experience loss of virologic response.

Labeling that may result from the study (ies):

Information regarding dosing, safety and activity in HIV-infected pediatric population.

Format of reports to be submitted:

Full study reports or interim clinical study reports, containing at least 6-month follow-up data, not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study (ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at <http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at <http://www.fda.gov/cder/guidance/6766fnl.pdf>*.

Timeframe for submitting reports of the study (ies):

Reports of the above studies must be submitted to the Agency on or before August 1, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your

submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

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We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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If you have any questions, contact Kenny Shade at 301-796-0807.

Sincerely yours,

Edward Cox, MD
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Edward Cox

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