20685/S041CRIXIVAN RSP

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-685/S-041

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
Sumneytown Pike,
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated August 27, 1999, received August 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan™ (indinavir sulfate) 200 mg, 333 mg, and 400 mg capsules.

We acknowledge receipt of your submissions dated March 13, and April 27, 2000, and February 8, 2001.

This supplemental new drug application provides for revisions to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the label.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted February 8, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-685/S-041." In addition, please provide a clean text MS Word version of the label as a desk copy. Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, call Christine Lincoln, RN, MS, MBA, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

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

/s/

Debra Birnkrant
3/21/01 01:32:33 PM
NDA 20-685/S-041

NDA: 20-685
S-041

Medical Officer's Review of Labeling Supplement

Date of submission: March 13, 2000
Date received: March 14, 2000
Date assigned: March 17, 2000
Date MOR completed: December 20, 2000

Applicant:	Merck Research Laboratories Sumneytown Pike West Point, PA 19486
Drug name:	Indinavir sulfate, MK-0639 Crixivan®
Dosage and Administration:	Oral 800 mg every 8 hours
Indication:	Treatment of HIV infection in adults
Reason for submission:	Amendment to Labeling supplement – 041
Background:	The original labeling supplement was submitted on August 27, 1999. An amendment was submitted on March 14, 2000, and additional information was provided by the applicant in a March 27, 2000 submission.
Related documents:	Supplemental application NDA 20-685/S-016, S-023, S-025, S-026, S-027, S-029, S-031, S-032, S-033, S-035, S-038, S-042. S-043

Resume:

The submitted material consists of a revised Warnings and Precautions Section of the package circular and a revised patient package insert for Crixivan® regarding both the interaction between Crixivan and sidenafil and the use of Crixivan in geriatric patients. This proposal is in accordance for the class labeling recommendations for all protease inhibitors.

Overview:

The original labeling supplement was submitted by the sponsor on August 27, 1999. An amendment to the labeling supplement was submitted on March 14, 2000 in response to Division comments sent by telephone facsimile. After additional comments from the Division, further information was provided by the sponsor in a March 27, 2000 submission.

Geriatric Use:

We agree with the proposed changes in the PRECAUTIONS, *Geriatric Use* section regarding the use of Crixivan in geriatric patients.

The coadministration of Crixivan and sildenafil:

Please include the following statement under CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification* Section:
Sildenafil: The results of one published study in HIV-infected men (n=6) indicated that coadministration of indinavir (800 mg indinavir every 8 hours chronically) with a single 25 mg dose of sildenafil resulted in an 11% increase in average $AUC_{0\text{-}8hr}$ of indinavir and a 48% increase in average indinavir peak concentration (C_{max}) compared to 800 mg q 8 hr alone. Average sildenafil AUC was increased by 340% following coadministration of sildenafil and indinavir compared to historical data following administration of sildenafil alone. (see PRECAUTIONS. Drug Interactions).

Please revise the PRECAUTIONS, *Drug Interactions, Erectile Dysfunction Agents* Section to read:
Particular caution should be used when prescribing sildenafil for patients receiving indinavir. The results of one published study in six HIV-infected subjects indicated that coadministration of indinavir (800 mg every 8 hours chronically) and sildenafil (25 mg as a single dose) resulted in increased indinavir and sildenafil concentrations. In two of the six subjects, prolonged clinical effects of sildenafil were noted for 72 hours after a single dose of sildenafil in combination with indinavir. Based on the results of this study, the dose of sildenafil should not exceed 25 mg in a 48-hour period. Patients receiving sildenafil should be advised that they are at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their health care providers (see WARNINGS).

We agree with the changes suggested in the WARNINGS, *Drug Interactions* Section and the PRECAUTIONS, *Information for Patients* Section as well as the proposed changes in the patient package insert.

Recommendation for Regulatory Action:
No regulatory action is required at this time. The sponsor will be informed of these proposed labeling changes via telephone facsimile. We look forward to the sponsor's response to our proposal.

Melisse S. Baylor, M.D.
Medical Officer, DAVDP

Concurrences:
HFD-530/Division Dir/DBirnkrant
HFD-530/MOTL/SKukich

Cc:
HFD-530/NDA 20-685
HFD-530/Division File
HFD-530/Pharm/Iyuen
HFD-530/BiopharmTL/KReynolds
HFD-530/Biopharm/RKumi
HFD-530/Chem/GLunn
HFD-530/Stat/Li
HFD-530/MOTL/SKukich
HFD-530/MO/MBaylor
HFD-530/CSO/CLincoln

APPEARS THIS WAY
ON ORIGINAL

/s/

Mellisse Baylor
12/20/00 01:43:36 PM
MEDICAL OFFICER

Stanka Kukich
12/20/00 02:14:14 PM
MEDICAL OFFICER

Debra Birnkrant
12/21/00 04:51:20 PM
MEDICAL OFFICER

Christine Lincoln
1/4/01 01:48:00 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

CSO Labeling Review

Date of Review: March 9, 2001

NDA Number: 20-685

Product Name: Crixivan (indinavir sulfate) 200 mg, 333 mg, and 400 mg capsules

Sponsor: Merck & Co., Inc.

Supplements: 041

Material Reviewed

Submission Date: February 8, 2001

Receipt Date: February 9, 2001

Background and Summary Description

This submission contains changes for supplement 041. This supplemental application provides for revisions to the **CLINICAL PHARMACOLOGY, WARNINGS,** and **PRECAUTIONS** sections of the label.

This package insert was compared electronically to the final printed labeling submitted December 7, 2000 (for supplements 030, 040, and 043).

Review - The revisions were as follows.

1. On page 4, **CLINICAL PHARMACOLOGY,** *Drug Interactions, Drugs that Require Dose Modification, Sildenafil:* (the following changes were made)

   a. Replacement of "q 8 hr" with "every 8 hours"
   b. Unbolding the cross-references to PRECAUTIONS
   c. Italicizing the cross-reference to the Drug Interaction subsection of PRECAUTIONS.
   d. The following paragraph was added:

Sildenafil: The results of one published study in HIV-infected men(n=6) indicated that coadministration of indinavir (800 mg every 8 hours chronically) with a single 25 mg-dose of sildenafil resulted in an 11% increase in average $AUC_{0\text{-}8hr}$ of indinavir and a 48% increase in average indinavir peak concentration (C_{max}) compared to 800 mg every 8 hours alone. Average sildenafil AUC was increased by 340% following coadministration of sildenafil and indinavir compared to historical data following administration of sildenafil alone (see PRECAUTIONS, *Drug Interactions*).

2. On page 11, under **WARNINGS**, *Drug interactions*, the following paragraph was added:

Particular caution should be used when prescribing sildenafil in patients receiving indinavir. Coadministration of CRIXIVAN with sildenafil is expected to substantially increase sildenafil plasma concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS, *Drug Interactions* and *Information for Patients*, and the manufacturer's complete prescribing information for sildenafil).

3. On Page 12, under **PRECAUTIONS**, *Information for patients,* the following paragraph was added:

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctors.

4. On page 13, under **PRECAUTIONS,** the following changes were made:

a. Unbolding the subsection heading and applying italics.
b. Cross-referencing CLINICAL PHARMACOLOGY, Drug Interactions.
c. The following paragraph was added:

Erectile Dysfunction Agents

Particular caution should be used when prescribing sildenafil for patients receiving indinavir. The results of one published study in six HIV-infected subjects indicated that coadministration of indinavir (800 mg every 8 hours chronically) and sildenafil (25 mg as a single dose) resulted in increased indinavir and sildenafil concentrations. In two of the six subjects, prolonged clinical effects of sildenafil were noted for 72 hours after a single dose of sildenafil in combination with indinavir. Based on the results of this study, the dose of sildenafil should not exceed 25 mg in a 48-hour period. Patients receiving sildenafil should be advised that they are at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their health care provider (see CLINICAL PHARMACOLOGY, *Drug Interactions* and WARNINGS).

5. On page 15, under **PRECAUTIONS**, the following section was added:

Geriatric Use

Clinical studies of CRIXIVAN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Conclusions

A supplement approval letter will be issued to the sponsor.

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

APPEARS THIS WAY
ON ORIGINAL

/s/

Christine Lincoln
3/20/01 11:46:30 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA: 20-685
S-041

Medical Officer's Review of Labeling Supplement

Date of submission: February 8, 2001
Date received: February 9, 2001
Date assigned: February 13, 2001
Date MOR completed: February 16, 2001

Applicant:	Merck Research Laboratories Sumneytown Pike West Point, PA 19486
Drug name:	Indinavir sulfate, MK-0639 Crixivan®
Dosage and Administration:	Oral 800 mg every 8 hours
Indication:	Treatment of HIV infection in adults
Reason for submission:	Amendment to Labeling Supplement – 041
Background:	The original labeling supplement was submitted on August 27, 1999 and amendments were submitted on March 13, 2000 and April 27, 2000.
Related documents:	Supplemental application NDA 20-685/S-016, S-023, S-025, S-026, S-027, S-029, S-031, S-032, S-033, S-035, S-038, S-042, S-043, S-045

Resume:

The submitted material consists of revised Clinical Pharmacology and Precautions sections regarding the interaction between Crixivan® and sildenafil.

Overview:

This labeling supplement was originally submitted on August 27, 1999 in accordance with class labeling recommendations for all protease inhibitors regarding the coadministration of protease inhibitors and sildenafil. Amendments to the labeling supplement were submitted on March 13, 2000 and April 27, 2000. According to the

Division's latest request dated December 20, 2000, the sponsor has revised the Clinical Pharmacology, *Drugs Requiring Dose Modification* section and the Precautions, *Drug Interactions* section to include information on changes in Crixivan and sildenafil plasma concentrations after coadministration of the two drugs.

Recommendation for Regulatory Action:

We agree with the proposed changes to the Crixivan label. The sponsor will be informed of this approval via telephone facsimile.

Melisse S. Baylor, M.D.
Medical Officer, DAVDP

Concurrences:
HFD-530/Division Dir/DBirnkrant
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Cc:
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HFD-530/Biopharm/RKumi
HFD-530/Chem/GLunn
HFD-530/MOTL/SKukich
HFD-530/MO/MBaylor
HFD-530/CSO/CLincoln

APPEARS THIS WAY
ON ORIGINAL

/s/

Mellisse Baylor
2/21/01 11:21:41 AM
MEDICAL OFFICER

Stanka Kukich
2/23/01 11:34:17 AM
MEDICAL OFFICER

Debra Birnkrant
2/23/01 12:55:52 PM
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Christine Lincoln
2/23/01 03:47:30 PM
CSO

APPEARS THIS WAY
ON ORIGINAL