CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020685/S022

Trade Name: CRIXIVAN

Generic Name: INDINAVIR SULFATE

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 12/17/98

Indication(s): TREATMENT OF ADULTS WITH HIV-1 INFECTIONS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020685/S022

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology/ Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020685/S022

APPROVAL LETTER

75

NDA 20-685/S-022

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

DEC 17 1998

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated June 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan® (indinavir sulfate).

We acknowledge receipt of your amendment dated:

October 13, 1998

The supplemental application provides for a new dosage strength, 333mg capsule, based on stability data derived from the currently approved 200 and 400mg capsules. The labeling changes will include addition of the new capsule strength to the Chemistry Section and the How Supplied Section of the package insert for Crixivan®. In addition, a new capsule strength will be added in Dosage Administration Section describing a dose increase of Crixivan to 1000mg (three 333mg capsules) when rifabutin and Crixivan are coadministered.

We have completed the review of this supplemental application, including the submitted draft labeling, 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 draft labeling submitted on June 16, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on June 16, 1998.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved supplemental NDA 20-685/S-022." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Terrie L. Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

/S/

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020685/S022

MEDICAL REVIEW(S)

NDA 20-685

DEC 18 1998

Medical Officer's Review of Chemistry Supplement

Date of submission: June 16, 1998
Date MOR competed: December 3, 1998

Applicant:	Merck Research Laboratories Sumneytown Pike West Point, PA 1986
Drug Name:	Indinavir sulfate, MK-0639 Crixavan®
Dosage and Administration:	Oral 800mg every 8 hours
Indication:	Treatment of HIV infection
Reason for Submission:	Chemistry Supplement-022
Background:	The original NDA was submitted on January 31, 1996. Crixivan® received accelerated approval on 3/13/96 and the traditional approval was granted on February 6, 1998.

Related Documents: Supplemental application NDA 20-685/S-016

Resume:

The submitted material consists of the revised Chemistry, How Supplied, Dosage and Administration Section of the package circular for Crixivan® to include a statement that Crixivan is available as 333 mg capsules in addition to 200 mg and 400 mg capsules.

Overview:
The sponsor proposes to market a 333 mg Crixivan® capsule, based on stability data derived from the currently approved 200 and 400 mg capsules. Crixivan® capsules, 333 mg will be manufactured using a weight multiple of the same granulation that is being used to produce the currently marketed 200 and 400 mg potency capsules. The 333 mg potency capsule will be produced according to the same essential manufacturing, packaging and testing procedures that are currently being utilized for the 200 mg and 400 mg potency capsules.

The labeling changes will include addition of new capsule strength to the Chemistry Section and the How Supplied Section of the package circular for Crixivan®. In addition, a new capsule strength will be added in the Dosage and Administration Section describing a dose increase of Crixivan to 1000 mg (three 333 mg capsules) when rifabutin and Crixivan are coadministered.

Recommendation for regulatory action:
Based on the submitted information in this supplemental application, it is acceptable to include the above listed dosage information in the package circular for Crixivan®.

/S/

Stanka Kukich, M.D.
Medical Officer, DAVDP

Concurrences:
HFD-530Division Dir/HJolson /S/ 12/18/98

cc:
HFD-530/NDA 20-685
HFD-530/Division file
HFD-530/Biopharm/KReynolds
HFD-530/Pharm/IYuen
HFD-530/Micro/NBattula
HFD-530/Chem/PLiu
HFD-530/MO/SKukich
HFD-530/CSO/TZeccola

c: NDA 20-685/SCF-022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020685/S022

CHEMISTRY REVIEW(S)

DEC 16 1998

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-685

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

4. AF NUMBER

5. SUPPLEMENT(S)

NUMBER(S)	DATE(S)
SCF-022	6/16/98

6. NAME OF DRUG
CRIXIVAN™ Capsules

7. NONPROPRIETARY NAME
indinavir sulfate capsules

8. SUPPLEMENT(S) PROVIDES FOR:
A 333 mg CRIXIVAN capsule.

9. AMENDMENTS / REPORTS
Submissions of 3/6/98 and 10/13/98

10. PHARMACOLOGICAL CATEGORY
Anti-HIV

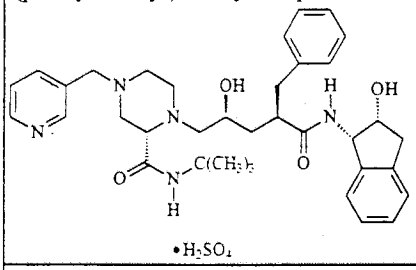
11. HOW DISPENSED
|X| Rx | | OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM(S)
Capsules

14. POTENCY(IES)
333 mg

15. CHEMICAL NAME AND STRUCTURE
[1(1S,2R),5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[[(-1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentonamide sulfate (1:1) salt



16. MEMORANDA

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The fill is the same as that for the currently marketed 200 mg and 400 mg capsules and the capsule shells are virtually identical. The container/closure system is the same as the currently approved package for the 200 mg and 400 mg capsules and the specifications and analytical methods are virtually the same. Stability is established by bracketing. The Supplement is reasonable and should, therefore, be approved.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
George Lunn. Ph.D.	/S/	7/1/98

20. CONCURRENCE: HFD-530/SMiller /S/ 12/16/98

DISTRIBUTION						
	X	Original Jacket	X	GLunn	X	AZeccola
	X	Division File	X	SMiller	X	SKukich
	X	HFD-830/CChen	X	IYuen	X	NBattula

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020685/S022

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 5 1998

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,685 (S-022)
Indinavir Sulfate (Crixivan™)
333 mg Capsules

Merck & Co. Inc.
P.O.Box 4, BLA-20
West Point, PA 19486

Reviewer: Vijay K. Tammara, Ph. D.

Submission Dates:
June 16, 1998
October 13, 1998

Indication: HIV infection

Type of Submission: Response to FDA Biowaiver Request

The sponsor is proposing to introduce a new 333-mg strength capsule that is bracketed by 200 and 400-mg strength capsules approved as part of the original NDA. This new strength is an exact multiple of 200 and 400-mg capsules. In this submission, the sponsor is requesting a biowaiver as per CFR 320.21 and provides documentation to support the request for the biowaiver for the 333-mg strength capsule of Indinavir sulfate.

The sponsor provided multi-point dissolution profiles for the 333mg capsules and compared with 200 and 400 mg capsules that were used in pivotal clinical trial. The 333-mg capsules meet the approved dissolution specification of Q = Further, the dissolution profiles were comparable and f_2 was found to be indicating similar dissolution profiles (Attachment 1).

Therefore, based on similar composition, solubility, similar dissolution profiles, and f_2 value approval for new 333 mg capsules can be granted.

RECOMMENDATION: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed this submission and recommends approval of new 333-mg capsules based on similar dissolution profiles and f_2 value > 50. Please, forward this Recommendation to the sponsor.

/S/ 11/5/98

Vijay K. Tammara, Ph. D.
Senior Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III, OCPB

Concurrence: /S/ 11/5/98

Kellie Reynolds, Pharm. D.
Acting Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

CC: HFD 530 /NDA 20,685
/MO/Kukich
/CSO/Zeccola
HFD 880 /Tammara
HFD 880 /TL/Reynolds
HFD 880 /DPE III
CDR /Barbara Murphy (for Drug files).

BEST POSSIBLE COPY

CRIXIVAN® (indinavir sulfate)
Chemical and Pharmaceutical Documentation
Response to the FDA

In support of a waiver for an *in vivo* bioequivalence study, dissolution profile data for CRIXIVAN® 333 mg potency capsules, lot number 802397, are presented in Table 1 below:

Table 1: Dissolution profile data for CRIXIVAN® 333 mg potency capsules, lot no. 802397

	Dissolution Data* (% dissolved)				
Location**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
1					
5					
10					
Mean					

* Specification: Q= minutes.
** Location 1 refers to samples collected at the beginning of encapsulating; location 5 refers to samples collected during the middle of location 10 refers to samples collected at the end of

The above dissolution profile data for the 333 mg potency capsule were compared to the dissolution profile data for the currently marketed potencies, 200 mg and 400 mg. Specifically, the average 333 mg dissolution profile data were compared to dissolution profile data for the following:

- A validation study lot for the 200 mg potency capsule, lot number 801591
- The 400 mg biobatch, lot number 0639DFC001E001
- Validation study lots for the 400 mg potency capsule, lot numbers 801593, 801594, and 801595.

The comparisons between dissolution profile data were performed using the following equation that defines the similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n\Sigma^{n}_{t=1}(R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

where R_t and T_t are the percent dissolved at each time point. According to this equation, an f_2 value suggests that the two dissolution profiles are similar.

Tables 2, 3, and 4 provide a summary of the comparative dissolution data for the 200 mg and 400 mg potency capsules. The f_2 values are provided following each table. The f_2 values are and suggest that the dissolution profile for the 333 mg capsule is similar to those for the 200 mg and 400 mg capsules.

Table 2: Comparison of the dissolution profile data for CRIXIVAN® 200 mg, lot no. 801591 and CRIXIVAN® 333 mg, lot no. 802397

	Dissolution Data (% dissolved)				
Potency/Lot Number	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
333 mg/802397					
200 mg/801591					

The f_2 value between the above profiles is

Table 3: Comparison of the dissolution profile data for CRIXIVAN® 400 mg, lot no. 0639DFC001E001 (biobatch) and CRIXIVAN® 333 mg, lot no. 802397

	Dissolution Data (% dissolved)				
Potency/Lot Number	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
333 mg/802397					
400mg/ 0639DFC001E001					

The f_2 value between the above profiles is

Table 4: Comparison of the dissolution profile data for CRIXIVAN® 400 mg, lot nos. 801593, 801594, 801595 and CRIXIVAN® 333 mg, lot no. 802397

	Dissolution Data (% dissolved)				
Potency/Lot Number	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
333 mg/802397					
400 mg/801593					
400 mg/801594					
400 mg/801595					
average* (400 mg)					

* The average was obtained using unrounded values.

The f_2 value between the average profile values for the three, 400 mg validation lots and Rx 802397 (333 mg) is

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020685/S022

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

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: SEP 25 1998

TO: Michelle W. Kloss, Ph.D.
Merck Research laboratories

FROM: Anthony M. Zeccola

THROUGH: Kellie Reynolds, Pharm.D., Biopharmceutics Team Leader /S/ 9/25/98
George Lunn, Ph.D., Chemist /S/ 9/25/98
Stephen Miller, Ph.D., Chemistry Team Leader /S/ 9/25/98

NDA: 20-685/S-022

SUBJECT: Biopharmaceutics Comments - Crixivan 333 mg capsules

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The following comment is being provided in response to your June 16, 1998 submission (S-022).

Because pharmacokinetic data have not been submitted for the 333 mg Crixivan capsules, please submit a formal request for a waiver of an in vivo bioequivalence study. Indicate the basis for the waiver, referring to 21 CFR 320.22(d)(2).

We are providing this 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.

/S/
Anthony M. Zeccola
Regulatory Management Officer
Division of Antiviral Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-685/S-022

JUN 19 1998

Merck Research Laboratories
P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486

Attention: Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kloss:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Crixivan® (Indinavir Sulfate)

NDA Number: 20-685

Supplement Number: S-022

Date of Supplement: June 16, 1998

Date of Receipt: June 17, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 16, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/ for AWD

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

ORIGINAL

NDA NO. 20-685 SUPPL NO. 22
NDA SUPPL FOR

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

These copies are OFFICIAL FDA Copies
not desk copies.

June 16, 1998

MERCK
Research Laboratories

Heidi M. Jolson, M.D., Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV, HFD-530 (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 17 1998

NDA 20-685: CRIXIVAN® (Indinavir Sulfate)

Supplemental New Drug Application

/S/
11/12/97

Dear Dr. Jolson:

Reference is made to the NDA cited above and to a January 27, 1998 submission outlining a proposal by MRL to file a supplemental application providing for a 333 mg CRIXIVAN capsule using bracketed stability data derived from the currently approved 200 mg and 400 mg CRIXIVAN capsules; this submission requested the Agency's concurrence with this proposal. Reference is also made to a February 26, 1998 facsimile communication from Mr. Anthony Zeccola (FDA) to Dr. Michelle Kloss (MRL) in which Agency comments regarding this proposal were provided and to a March 6, 1998 submission which provided responses to these Agency comments. Additional reference is made to a March 25, 1998 telephone conversation between Mr. Zeccola and Dr. Kloss during which Mr. Zeccola confirmed that the Agency was in agreement with this proposal.

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (b), we submit a supplement to NDA 20-685.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes to the Chemistry and Labeling Section(s) of the approved New Drug Application for CRIXIVAN® and provides documentation in support of a 333 mg CRIXIVAN capsule.

Attached with this letter are the following:

- Chemistry and Pharmaceutical Manufacturing and Control Documentation
- Summary of revisions for the circular
- Draft bottle label
- Annotated circular, illustrating the revisions
- Clean running text of the circular
- Diskette containing the zipped file of the annotated circular
- Diskette containing the zipped file of the clean circular

In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

Pursuant to 21 CFR 314.70(a), a complete field copy of this supplement has been submitted to the FDA Philadelphia District Office.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely yours,

Larry P Bell for

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Attachments
Q:\YARBROUGH\LAC\CRIXIVAN\NDA20865

Desk Copy(2) w/diskettes: Mr. Anthony Zeccola, HFD-530, Federal Express #1

Desk Copy: Philadelphia District Office, FDA, U.S. Custom House
Room 900, 2nd & Chestnut Streets, Philadelphia, PA 19106-2973
Federal Express #2