CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-685 / S-046, S-047

Trade Name: Crixivan

Generic Name: (indinavir sulfate)

Sponsor: Merck & Co.

Approval Date: May 7, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	**X**
Labeling	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	**X**
Administrative and Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-685/S-046 and S-047

Merck & Co., Inc.
Attention: Sandra Rattray, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 2000, RY 33-720
Rahway, NJ 07065

Dear Dr. Rattray:

Please refer to your supplemental new drug applications dated June 20, 2003, received June 23, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan® (indinavir sulfate) capsules.

We acknowledge receipt of your submissions dated October 27, 2003, February 6, 2004, and February 24, 2004.

This supplemental new drug application provides for the following changes:

1. Revisions to the Clinical Pharmacology, Warnings, Precautions, and Dosage and Administration sections of the package insert.

2. Revisions to the "Can Crixivan be taken with other medications?" and "What are the possible side effects of Crixivan?" sections of the patient package insert.

We have completed the review of these supplemental applications, 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 enclosed 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 enclosed labeling (text for the package insert and patient package insert).

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 heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-685/S-046

and S-047." 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

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, call Virginia L. Behr, Chief, Project Management Staff, 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

Enclosure: approved draft labeling (package insert and patient package insert).

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

/s/

Jeffrey Murray
5/7/04 02:42:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-685/ S-046 and S-047

Merck and Company, Inc.
Attention: Sandra Rattray, Ph.D., Regulatory Affairs
P.O.Box 2000, RY33-720
Rahway, New Jersey 07065

Dear Dr. Rattray,

Please refer to your supplemental new drug applications dated March 30, 2000 and June 9, 2000, received April 3, 2000 and June 12, 2000 respectively, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan™ (indinavir sulfate).

We acknowledge receipt of your submissions dated December 14, 2001, January 22, 2002, July 10, 2002, and July 15, 2002 to your supplemental new drug application dated March 30, 2000. We also acknowledge receipt of your submissions dated April 11, 2001, May 22, 2001, December 14, 2001, January 22, 2002, July 10, 2002, and July 15, 2002 to your supplemental new drug application dated June 9, 2000.

We also acknowledge receipt of your submission dated April 23, 2003. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

These supplemental new drug applications provide for labeling revisions to the Precautions, *Drug Interactions* section and inclusion of indinavir/ritonavir pharmacokinetic information.

We completed our review of these applications, as amended, and they are approvable. Before the applications may be approved, however, you must address the following deficiencies:

1. Provide a scientific rationale that supports your position that inhibition of CYP3A metabolism has a similar clinical impact for atorvastatin as it does for lovastatin and simvastatin.

2. Submit clinical study reports for drug interactions between indinavir and theophylline (Protocol 049) and between indinavir and saquinavir (Protocol 051).

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not

follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, call Virginia L. Yoerg, Regulatory Health 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

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

/s/

Jeffrey Murray
4/30/03 03:39:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

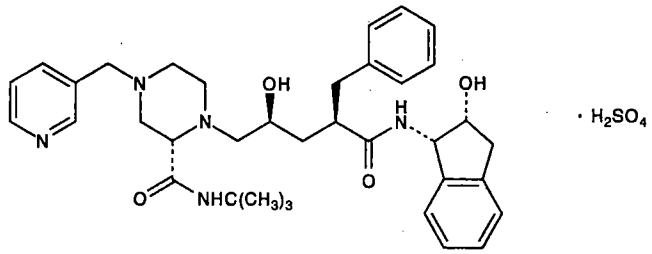
LABELING

CRIXIVAN®
(INDINAVIR SULFATE)
CAPSULES

DESCRIPTION

CRIXIVAN* (indinavir sulfate) is an inhibitor of the human immunodeficiency virus (HIV) protease. CRIXIVAN Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulfate.

The chemical name for indinavir sulfate is [1(1*S*,2*R*),5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-*erythro*-pentonamide sulfate (1:1) salt. Indinavir sulfate has the following structural formula:



Indinavir sulfate is a white to off-white, hygroscopic, crystalline powder with the molecular formula $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ and a molecular weight of 711.88. It is very soluble in water and in methanol.

MICROBIOLOGY

Mechanism of Action: HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1. Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles.

Antiretroviral Activity In Vitro: The *in vitro* activity of indinavir was assessed in cell lines of lymphoblastic and monocytic origin and in peripheral blood lymphocytes. HIV-1 variants used to infect the different cell types include laboratory-adapted variants, primary clinical isolates and clinical isolates resistant to nucleoside analogue and nonnucleoside inhibitors of the HIV-1 reverse transcriptase. The IC_{95} (95% inhibitory concentration) of indinavir in these test systems was in the range of 25 to 100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, indinavir showed synergistic activity in cell culture. The relationship between *in vitro* susceptibility of HIV-1 to indinavir and inhibition of HIV-1 replication in humans has not been established.

Drug Resistance: Isolates of HIV-1 with reduced susceptibility to the drug have been recovered from some patients treated with indinavir. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral

*Registered trademark of MERCK & CO., Inc.

protease. Eleven amino acid residue positions, (L10I/V/R, K20I/M/R, L24I, M46I/L, I54A/V, L63P, I64V, A71T/V, V82A/F/T, I84V, and L90M), at which substitutions are associated with resistance, have been identified. Resistance was mediated by the co-expression of multiple and variable substitutions at these positions. No single substitution was either necessary or sufficient for measurable resistance (≥4-fold increase in IC_{95}). In general, higher levels of resistance were associated with the co-expression of greater numbers of substitutions, although their individual effects varied and were not additive. At least 3 amino acid substitutions must be present for phenotypic resistance to indinavir to reach measurable levels. In addition, mutations in the p7/ p1 and p1/ p6 gag cleavage sites were observed in some indinavir resistant HIV-1 isolates.

In vitro phenotypic susceptibilities to indinavir were determined for 38 viral isolates from 13 patients who experienced virologic rebounds during indinavir monotherapy. Pre-treatment isolates from five patients exhibited indinavir IC_{95} values of 50-100 nM. At or following viral RNA rebound (after 12-76 weeks of therapy), IC_{95} values ranged from 25 to >3000 nM, and the viruses carried 2 to 10 mutations in the protease gene relative to baseline.

Cross-Resistance to Other Antiviral Agents: Varying degrees of HIV-1 cross-resistance have been observed between indinavir and other HIV-1 protease inhibitors. In studies with ritonavir, saquinavir, and amprenavir, the extent and spectrum of cross-resistance varied with the specific mutational patterns observed. In general, the degree of cross-resistance increased with the accumulation of resistance-associated amino acid substitutions. Within a panel of 29 viral isolates from indinavir-treated patients that exhibited measurable (≥4-fold) phenotypic resistance to indinavir, all were resistant to ritonavir. Of the indinavir resistant HIV-1 isolates, 63% showed resistance to saquinavir and 81% to amprenavir.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration (T_{max}) of 0.8 ± 0.3 hours (mean ± S.D.) (n=11). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-1000 mg dose range. At a dosing regimen of 800 mg every 8 hours, steady-state area under the plasma concentration time curve (AUC) was 30,691 ± 11,407 nM•hour (n=16), peak plasma concentration (C_{max}) was 12,617 ± 4037 nM (n=16), and plasma concentration eight hours post dose (trough) was 251 ± 178 nM (n=16).

Effect of Food on Oral Absorption: Administration of indinavir with a meal high in calories, fat, and protein (784 kcal, 48.6 g fat, 31.3 g protein) resulted in a 77% ± 8% reduction in AUC and an 84% ± 7% reduction in C_{max} (n=10). Administration with lighter meals (e.g., a meal of dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) resulted in little or no change in AUC, C_{max} or trough concentration.

Distribution: Indinavir was approximately 60% bound to human plasma proteins over a concentration range of 81 nM to 16,300 nM.

Metabolism: Following a 400-mg dose of ^{14}C-indinavir, 83 ± 1% (n=4) and 19 ± 3% (n=6) of the total radioactivity was recovered in feces and urine, respectively; radioactivity due to parent drug in feces and urine was 19.1% and 9.4%, respectively. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies indicate that cytochrome P-450 3A4 (CYP3A4) is the major enzyme responsible for formation of the oxidative metabolites.

Elimination: Less than 20% of indinavir is excreted unchanged in the urine. Mean urinary excretion of unchanged drug was 10.4 ± 4.9% (n=10) and 12.0 ± 4.9% (n=10) following a single 700-mg and 1000-mg dose, respectively. Indinavir was rapidly eliminated with a half-life of 1.8 ± 0.4 hours (n=10). Significant accumulation was not observed after multiple dosing at 800 mg every 8 hours.

Special Populations

Hepatic Insufficiency: Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of indinavir resulting in

approximately 60% higher mean AUC following a single 400-mg dose (n=12). The half-life of indinavir increased to 2.8 ± 0.5 hours. Indinavir pharmacokinetics have not been studied in patients with severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*).

Renal Insufficiency: The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency.

Gender: The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received CRIXIVAN 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for one week. Indinavir pharmacokinetic parameters in these women were compared to those in HIV seropositive men (pooled historical control data). Differences in indinavir exposure, peak concentrations, and trough concentrations between males and females are shown in Table 1 below:

Table 1

PK Parameter	% change in PK parameter for females relative to males	90% Confidence Interval
$AUC_{0\text{-}8h}$ (nM•hr)	↓13%	(↓32%, ↑12%)
C_{max} (nM)	↓13%	(↓32%, ↑10%)
C_{8h} (nM)	↓22%	(↓47%, ↑15%)

↓Indicates a decrease in the PK parameter; ↑indicates an increase in the PK parameter.

The clinical significance of these gender differences in the pharmacokinetics of indinavir is not known.

Race: Pharmacokinetics of indinavir appear to be comparable in Caucasians and Blacks based on pharmacokinetic studies including 42 Caucasians (26 HIV-positive) and 16 Blacks (4 HIV-positive).

Pediatric: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m² every 8 hours, produced $AUC_{0\text{-}8hr}$ of 38,742 ± 24,098 nM•hour (n=34), C_{max} of 17,181 ± 9809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

Drug Interactions (also see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, *Drug Interactions*)

Indinavir is an inhibitor of the cytochrome P450 isoform CYP3A4. Coadministration of CRIXIVAN and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see CONTRAINDICATIONS and WARNINGS). Based on *in vitro* data in human liver microsomes, indinavir does not inhibit CYP1A2, CYP2C9, CYP2E1 and CYP2B6. However, indinavir may be a weak inhibitor of CYP2D6.

Indinavir is metabolized by CYP3A4. Drugs that induce CYP3A4 activity would be expected to increase the clearance of indinavir, resulting in lowered plasma concentrations of indinavir. Coadministration of CRIXIVAN and other drugs that inhibit CYP3A4 may decrease the clearance of indinavir and may result in increased plasma concentrations of indinavir.

Drug interaction studies were performed with CRIXIVAN and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of CRIXIVAN on the AUC, C_{max} and C_{min} are summarized in Table 2

(effect of other drugs on indinavir) and Table 3 (effect of indinavir on other drugs). For information regarding clinical recommendations, see Table 9 in PRECAUTIONS.

Table 2
Drug Interactions: Pharmacokinetic Parameters for Indinavir in the Presence of the Coadministered Drug
(See PRECAUTIONS, Table 9 for Recommended Alterations in Dose or Regimen)

Coadministered drug	Dose of Coadministered drug (mg)	Dose of CRIXIVAN (mg)	n	Ratio (with/without coadministered drug) of Indinavir Pharmacokinetic Parameters (90% CI); No Effect =1.00		
				C_{max}	AUC	C_{min}
Cimetidine	600 twice daily, 6 days	400 single dose	12	1.07 (0.77, 1.49)	0.98 (0.81, 1.19)	0.82 (0.69, 0.99)
Clarithromycin	500 q12h, 7 days	800 three times daily, 7 days	10	1.08 (0.85, 1.38)	1.19 (1.00, 1.42)	1.57 (1.16, 2.12)
Delavirdine	400 three times daily	400 three times daily, 7 days	28	0.64[1] (0.48, 0.86)	No significant change[1]	2.18[1] (1.16, 4.12)
Delavirdine	400 three times daily	600 three times daily, 7 days	28	No significant change	1.53[1] (1.07, 2.20)	3.98[1] (2.04, 7.78)
Efavirenz[2]	600 once daily, 10 days	1000 three times daily, 10 days	20			
		After morning dose		No significant change[1]	0.67[1] (0.61, 0.74)	0.61[1] (0.49, 0.76)
		After afternoon dose		No significant change[1]	0.63[1] (0.54, 0.74)	0.48[1] (0.43, 0.53)
		After evening dose		0.71[1] (0.57, 0.89)	0.54[1] (0.46, 0.63)	0.43[1] (0.37, 0.50)
Fluconazole[2]	400 once daily, 8 days	1000 three times daily, 7 days	11	0.87 (0.72, 1.05)	0.76 (0.59, 0.98)	0.90 (0.72, 1.12)
Grapefruit Juice	8 oz.	400 single dose	10	0.65 (0.53, 0.79)	0.73 (0.60, 0.87)	0.90 (0.71, 1.15)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 7 days	11	0.95 (0.88, 1.03)	0.99 (0.87, 1.13)	0.89 (0.75, 1.06)
Itraconazole	200 twice daily, 7 days	600 three times daily, 7 days	12	0.78[3] (0.69, 0.88)	0.99[3] (0.91, 1.06)	1.49[3] (1.28, 1.74)
Ketoconazole	400 once daily, 7 days	600 three times daily, 7 days	10	1.14[3] (0.93, 1.40)	1.62[3] (1.38, 1.92)	2.80[3] (2.20, 3.57)
Methadone	20-60 once daily in the morning, 8 days	800 three times daily, 8 days	10	See text below for discussion of interaction.		
Quinidine	200 single dose	400 single dose	10	0.96 (0.79, 1.18)	1.07 (0.89, 1.28)	0.93 (0.73, 1.19)
Rifabutin	150 once daily in the morning, 10 days	800 three times daily, 10 days	14	0.80 (0.72, 0.89)	0.68 (0.60, 0.76)	0.60 (0.51, 0.72)
Rifabutin	300 once daily in the morning, 10 days	800 three times daily, 10 days	10	0.75 (0.61, 0.91)	0.66 (0.56, 0.77)	0.61 (0.50, 0.75)
Rifampin	600 once daily in the morning, 8 days	800 three times daily, 7 days	12	0.13 (0.08, 0.22)	0.08 (0.06, 0.11)	Not Done
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 16[3]	See text below for discussion of interaction.		
Ritonavir	200 twice daily, 14 days	800 twice daily, 14 days	9, 16[3]	See text below for discussion of interaction.		
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
St. John's wort (*Hypericum perforatum*, standardized to 0.3 % hypericin)	300 three times daily with meals, 14 days	800 three times daily	8	Not Available	0.46 (0.34, 0.58)[4]	0.19 (0.06, 0.33)[4]
Stavudine (d4T)[2]	40 twice daily, 7	800 three times	11	0.95	0.95	1.13

	days	daily, 7 days		(0.80, 1.11)	(0.80, 1.12)	(0.83, 1.53)
Trimethoprim/ Sulfamethoxazole	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 four times daily, 7 days	12	1.12 (0.87, 1.46)	0.98 (0.81, 1.18)	0.83 (0.72, 0.95)
Zidovudine[2]	200 three times daily, 7 days	1000 three times daily, 7 days	12	1.06 (0.91, 1.25)	1.05 (0.86, 1.28)	1.02 (0.77, 1.35)
Zidovudine/Lamivudine (3TC)[2]	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 9[5]	1.05 (0.83, 1.33)	1.04 (0.67, 1.61)	0.98 (0.56, 1.73)

All interaction studies conducted in healthy, HIV-negative adult subjects, unless otherwise indicated.
[1] Relative to indinavir 800 mg three times daily alone.
[2] Study conducted in HIV-positive subjects.
[3] Comparison to historical data on 16 subjects receiving indinavir alone.
[4] 95% CI.
[5] Parallel group design; n for indinavir + coadministered drug, n for indinavir alone.

Table 3

Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Indinavir

(See PRECAUTIONS, Table 9 for Recommended Alterations in Dose or Regimen)

Coadministered drug	Dose of Coadministered drug (mg)	Dose of CRIXIVAN (mg)	n	Ratio (with/without CRIXIVAN) of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect =1.00		
				C_{max}	AUC	C_{min}
Clarithromycin	500 twice daily, 7 days	800 three times daily, 7 days	12	1.19 (1.02, 1.39)	1.47 (1.30, 1.65)	1.97 (1.58, 2.46) n=11
Efavirenz	200 once daily, 14 days	800 three times daily, 14 days	20	No significant change	No significant change	--
Ethinyl Estradiol (ORTHO-NOVUM 1/35)	35 mcg, 8 days	800 three times daily, 8 days	18	1.02 (0.96, 1.09)	1.22 (1.15, 1.30)	1.37 (1.24, 1.51)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 8 days	11	1.34 (1.12, 1.60)	1.12 (1.03, 1.22)	1.00 (0.92, 1.08)
Methadone[2]	20-60 once daily in the morning, 8 days	800 three times daily, 8 days	12	0.93 (0.84, 1.03)	0.96 (0.86, 1.06)	1.06 (0.94, 1.19)
Norethindrone (ORTHO-NOVUM 1/35)	1 mcg, 8 days	800 three times daily, 8 days	18	1.05 (0.95, 1.16)	1.26 (1.20, 1.31)	1.44 (1.32, 1.57)
Rifabutin *150 mg once daily in the morning, 11 days + indinavir compared to 300 mg once daily in the morning, 11 days alone	150 once daily in the morning, 10 days	800 three times daily, 10 days	14	1.29 (1.05, 1.59)	1.54 (1.33, 1.79)	1.99 (1.71, 2.31) n=13
	300 once daily in the morning, 10 days	800 three times daily, 10 days	10	2.34 (1.64, 3.35)	2.73 (1.99, 3.77)	3.44 (2.65, 4.46) n=9
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 4[3]	1.61 (1.13, 2.29)	1.72 (1.20, 2.48)	1.62 (0.93, 2.85)
	200 twice daily, 14 days	800 twice daily, 14 days	9, 5[3]	1.19 (0.85, 1.66)	1.96 (1.39, 2.76)	4.71 (2.66, 8.33) n=9, 4
Saquinavir						
Hard gel formulation	600 single dose	800 three times daily, 2 days	6	4.7 (2.7, 8.1)	6.0 (4.0, 9.1)	2.9 (1.7, 4.7)[4]
Soft gel formulation	800 single dose	800 three times daily, 2 days	6	6.5 (4.7, 9.1)	7.2 (4.3, 11.9)	5.5 (2.2, 14.1)[4]

Soft gel formulation	1200 single dose	800 three times daily, 2 days	6	4.0 (2.7, 5.9)	4.6 (3.2, 6.7)	5.5 (3.7, 8.3)[4]
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
Stavudine[1]	40 twice daily, 7 days	800 three times daily, 7 days	13	0.86 (0.73, 1.03)	1.21 (1.09, 1.33)	Not Done
Theophylline	250 single dose (on Days 1 and 7)	800 three times daily, 6 days (Days 2 to 7)	12, 4[3]	0.88 (0.76, 1.03)	1.14 (1.04, 1.24)	1.13 (0.86, 1.49) n=7, 3
Trimethoprim/ Sulfamethoxazole						
Trimethoprim	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 q6h, 7 days	12	1.18 (1.05, 1.32)	1.18 (1.05, 1.33)	1.18 (1.00, 1.39)
Trimethoprim/ Sulfamethoxazole						
Sulfamethoxazole	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 q6h, 7 days	12	1.01 (0.95, 1.08)	1.05 (1.01, 1.09)	1.05 (0.97, 1.14)
Vardenafil	2.5 single dose	800 three times daily	18	See text below for discussion of interaction.		
Zidovudine[1]	200 three times daily, 7 days	1000 three times daily, 7 days	12	0.89 (0.73, 1.09)	1.17 (1.07, 1.29)	1.51 (0.71, 3.20) n=4
Zidovudine/Lamivudine[1]						
Zidovudine	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 7[3]	1.23 (0.74, 2.03)	1.39 (1.02, 1.89)	1.08 (0.77, 1.50) n=5, 5
Zidovudine/Lamivudine[1]						
Lamivudine	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 7[3]	0.73 (0.52, 1.02)	0.91 (0.66, 1.26)	0.88 (0.59, 1.33)

All interaction studies conducted in healthy, HIV-negative adult subjects, unless otherwise indicated.
[1] Study conducted in HIV-positive subjects.
[2] Study conducted in subjects on methadone maintenance.
[3] Parallel group design; n for coadministered drug + indinavir, n for coadministered drug alone.
[4] C_{6hr}

Delavirdine: Delavirdine inhibits the metabolism of indinavir such that coadministration of 400-mg or 600-mg indinavir three times daily with 400-mg delavirdine three times daily alters indinavir AUC, C_{max} and C_{min} (see Table 2). Indinavir had no effect on delavirdine pharmacokinetics (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Delavirdine*), based on a comparison to historical delavirdine pharmacokinetic data.

Methadone: Administration of indinavir (800 mg every 8 hours) with methadone (20 mg to 60 mg daily) for one week in subjects on methadone maintenance resulted in no change in methadone AUC. Based on a comparison to historical data, there was little or no change in indinavir AUC.

Ritonavir: Compared to historical data in patients who received indinavir 800 mg every 8 hours alone, twice-daily coadministration to volunteers of indinavir 800 mg and ritonavir with food for two weeks resulted in an 2.7-fold increase of indinavir AUC_{24h}, a 1.6-fold increase in indinavir C_{max}, and an 11-fold increase in indinavir C_{min} for a 100-mg ritonavir dose and a 3.6-fold increase of indinavir AUC_{24h}, a 1.8-fold increase in indinavir C_{max}, and a 24-fold increase in indinavir C_{min}

for a 200-mg ritonavir dose. In the same study, twice-daily coadministration of indinavir (800 mg) and ritonavir (100 or 200 mg) resulted in ritonavir AUC_{24h} increases versus the same doses of ritonavir alone (see Table 3).

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 WARNINGS, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

Vardenafil: Indinavir (800 mg every 8 hours) coadministered with a single 10-mg dose of vardenafil resulted in a 16-fold increase in vardenafil AUC, a 7-fold increase in vardenafil C_{max}, and a 2-fold increase in vardenafil half-life (see WARNINGS, *Drug Interactions* and PRECAUTIONS, *Drug Interactions*).

INDICATIONS AND USAGE

CRIXIVAN in combination with antiretroviral agents is indicated for the treatment of HIV infection.

This indication is based on two clinical trials of approximately 1 year duration that demonstrated: 1) a reduction in the risk of AIDS-defining illnesses or death; 2) a prolonged suppression of HIV RNA.

Description of Studies

In all clinical studies, with the exception of ACTG 320, the AMPLICOR HIV MONITOR assay was used to determine the level of circulating HIV RNA in serum. This is an experimental use of the assay. HIV RNA results should not be directly compared to results from other trials using different HIV RNA assays or using other sample sources.

Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of CRIXIVAN in combination with zidovudine and lamivudine with that of zidovudine plus lamivudine on the progression to an AIDS-defining illness (ADI) or death. Patients were protease inhibitor and lamivudine naive and zidovudine experienced, with CD4 cell counts of ≤200 cells/mm^3. The study enrolled 1156 HIV-infected patients (17% female, 28% Black, 18% Hispanic, mean age 39 years). The mean baseline CD4 cell count was 87 cells/mm^3. The mean baseline HIV RNA was 4.95 $\log_{10}$ copies/mL (89,035 copies/mL). The study was terminated after a planned interim analysis, resulting in a median follow-up of 38 weeks and a maximum follow-up of 52 weeks. Results are shown in Table 4 and Figures 1 & 2.

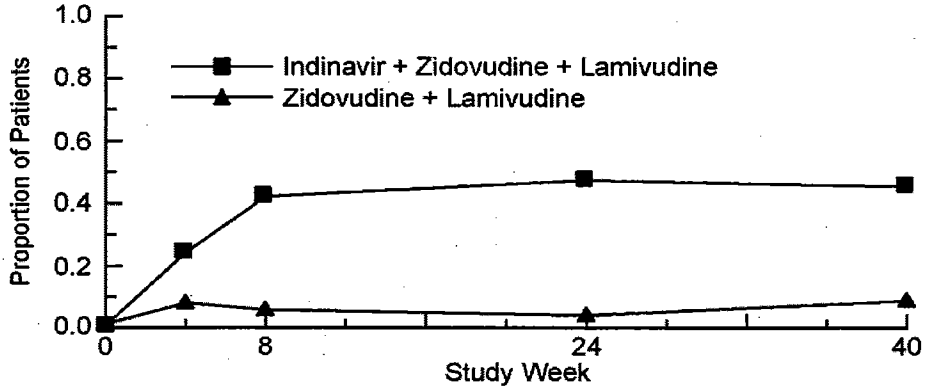
Table 4
ACTG 320

Endpoint	Number (%) of Patients with AIDS-defining Illness or Death	
	IDV+ZDV+L (n=577)	ZDV+L (n=579)
HIV Progression or Death	35 (6.1)	63 (10.9)
Death*	10 (1.7)	19 (3.3)

*The number of deaths is inadequate to assess the impact of Indinavir on survival.
IDV = Indinavir, ZDV = Zidovudine, L = Lamivudine

Study ACTG 320: Figure 1

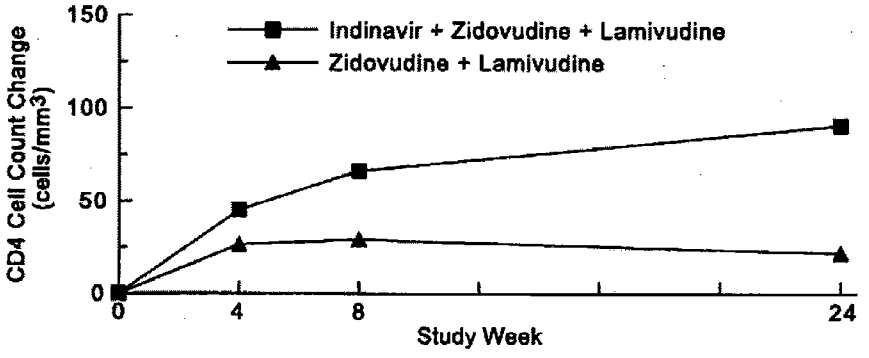
Indinavir Protocol ACTG 320 Zidovudine Experienced
Plasma Viral RNA - Proportions Below 400 copies/mL



	N	N	N
IDV+ZDV+L	566	437	218
ZDV+L	573	450	231

Study ACTG 320: Figure 2

ACTG 320 Zidovudine Experienced
CD4 Cell Counts - Mean Change from Baseline



	N	N	N
IDV + ZDV + L	577	522	417
ZDV + L	579	512	423

Study 028, a double-blind, multicenter, randomized, clinical endpoint trial conducted in Brazil, compared the effects of CRIXIVAN plus zidovudine with those of CRIXIVAN alone or zidovudine alone on the progression to an ADI or death, and on surrogate marker responses. All patients were antiretroviral naive with CD4 cell counts of 50 to 250 cells/mm^3. The study enrolled 996 HIV-1 seropositive patients [28% female, 11% Black, 1% Asian/Other, median age 33 years, mean baseline CD4 cell count of 152 cells/mm^3, mean serum viral RNA of 4.44 $\log_{10}$ copies/mL (27,824 copies/mL)]. Treatment regimens containing zidovudine were modified in a blinded manner with the optional addition of lamivudine (median time: week 40). The median length of follow-up was 56 weeks with a maximum of 97 weeks. The study was terminated after a planned

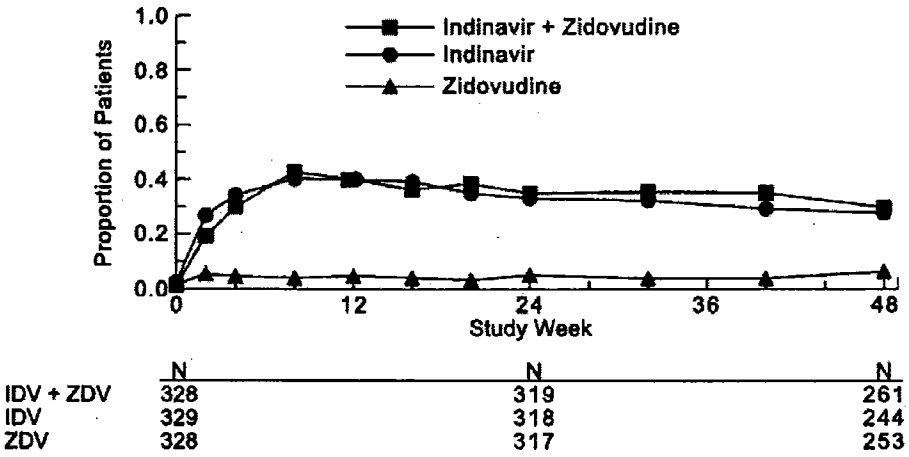
interim analysis, resulting in a median follow-up of 56 weeks and a maximum follow-up of 97 weeks. Results are shown in Table 5 and Figures 3 and 4.

Table 5
Protocol 028

Endpoint	Number (%) of Patients with AIDS-defining Illness or Death		
	IDV+ZDV (n=332)	IDV (n=332)	ZDV (n=332)
HIV Progression or Death	21 (6.3)	27 (8.1)	62 (18.7)
Death*	8 (2.4)	5 (1.5)	11 (3.3)

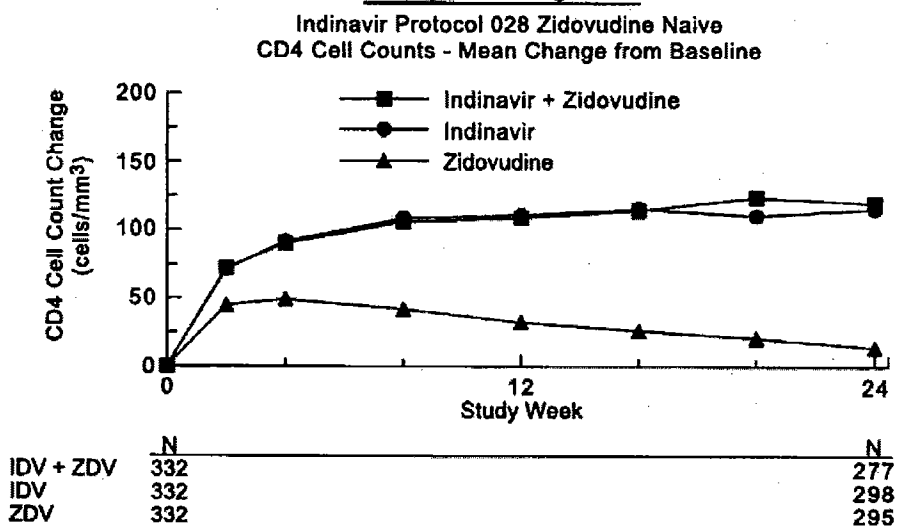
*The number of deaths is inadequate to assess the impact of Indinavir on survival.

Study 028: Figure 3



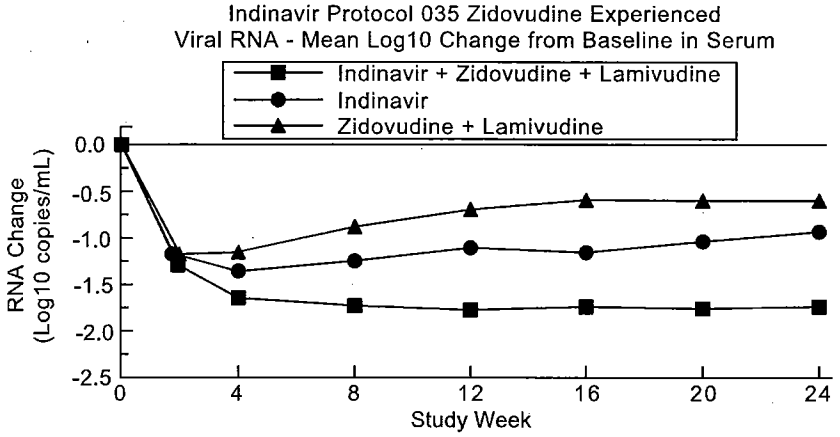
	N	N	N
IDV + ZDV	328	319	261
IDV	329	318	244
ZDV	328	317	253

Study 028: Figure 4



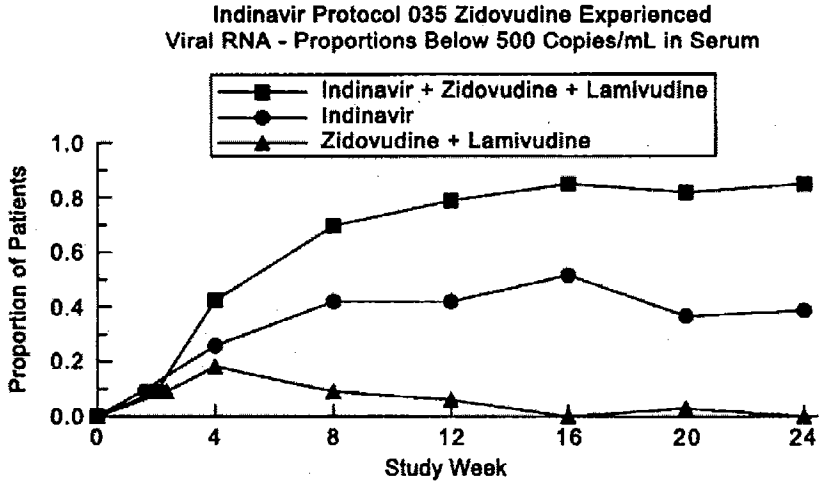
Study 035 was a multicenter, randomized trial in 97 HIV-1 seropositive patients who were zidovudine-experienced (median exposure 30 months), protease-inhibitor- and lamivudine-naive, with mean baseline CD4 count 175 cells/mm^3 and mean baseline serum viral RNA 4.62 $\log_{10}$ copies/mL (41,230 copies/mL). Comparisons included CRIXIVAN plus zidovudine plus lamivudine vs. CRIXIVAN alone vs. zidovudine plus lamivudine. After at least 24 weeks of randomized, double-blind therapy, patients were switched to open-label CRIXIVAN plus lamivudine plus zidovudine. Mean changes in $\log_{10}$ viral RNA in serum, the proportions of patients with viral RNA below 500 copies/mL in serum, and mean changes in CD4 cell counts, during 24 weeks of randomized, double-blinded therapy are summarized in Figures 5, 6, and 7, respectively. A limited number of patients remained on randomized, double-blind treatment for longer periods; based on this extended treatment experience, it appears that a greater number of subjects randomized to CRIXIVAN plus zidovudine plus lamivudine demonstrated HIV RNA levels below 500 copies/mL during one year of therapy as compared to those in other treatment groups.

Study 035: Figure 5

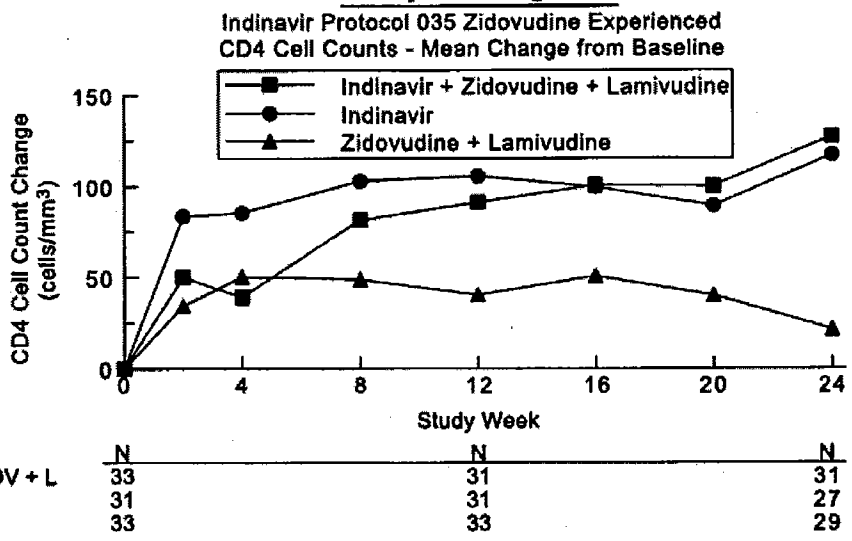


	N	N	N
IDV + ZDV + L	32	30	30
IDV	31	31	28
ZDV + L	33	33	30

Study 035: Figure 6



Study 035: Figure 7



	N	N	N
IDV + ZDV + L	33	31	31
IDV	31	31	27
ZDV + L	33	33	29

Genotypic Resistance in Clinical Studies

Study 006 (10/15/93-10/12/94) was a dose-ranging study in which patients were initially treated with CRIXIVAN at a dose of <2.4 g/day followed by 2.4 g/day. Study 019 (6/23/94-4/10/95) was a randomized comparison of CRIXIVAN 600 mg every 6 hours, CRIXIVAN plus zidovudine, and zidovudine alone. Table 6 shows the incidence of genotypic resistance at 24 weeks in these studies.

Table 6
Genotypic Resistance at 24 Weeks

Treatment Group	Resistance to IDV n/N*	Resistance to ZDV n/N*
IDV	—	—
<2.4 g/day	31/37 (84%)	—
2.4 g/day	9/21 (43%)	1/17 (6%)
IDV/ZDV	4/22 (18%)	1/22 (5%)
ZDV	1/18 (6%)	11/17 (65%)

*N - includes patients with non-amplifiable virus at 24 weeks who had amplifiable virus at week 0.

CONTRAINDICATIONS

CRIXIVAN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Inhibition of CYP3A4 by CRIXIVAN can result in elevated plasma concentrations of the following drugs, potentially causing serious or life-threatening reactions:

Table 7
Drug Interactions With Crixivan: Contraindicated Drugs

Drug Class	Drugs Within Class That Are Contraindicated With CRIXIVAN
Antiarrhythmics	amiodarone
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
Sedative/hypnotics	midazolam, triazolam
GI motility agents	cisapride
Neuroleptics	pimozide

WARNINGS

ALERT: Find out about medicines that should not be taken with CRIXIVAN. This statement is included on the product's bottle label.

Nephrolithiasis/Urolithiasis

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN therapy. The cumulative frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (12.4%; range across individual trials: 4.7% to 34.4%). The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN; however, the risk over time remains relatively constant. In some cases, nephrolithiasis/urolithiasis has been associated with renal insufficiency or acute renal failure, pyelonephritis with or without bacteremia. If signs or symptoms of nephrolithiasis/urolithiasis occur, (including flank pain, with or without hematuria or microscopic hematuria), temporary interruption (e.g., 1-3 days) or discontinuation of therapy may be considered. **Adequate hydration is recommended in all patients treated with CRIXIVAN. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION, *Nephrolithiasis/Urolithiasis*.)**

Hemolytic Anemia

Acute hemolytic anemia, including cases resulting in death, has been reported in patients treated with CRIXIVAN. Once a diagnosis is apparent, appropriate measures for the treatment of hemolytic anemia should be instituted, including discontinuation of CRIXIVAN.

Hepatitis

Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with CRIXIVAN. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapy(ies), a causal relationship between CRIXIVAN and these events has not been established.

Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Drug Interactions

Concomitant use of CRIXIVAN with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV

protease inhibitors, including CRIXIVAN, are used in combination with these drugs (see PRECAUTIONS, *Drug Interactions*).

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

Concomitant use of CRIXIVAN and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Coadministration of CRIXIVAN and St. John's wort has been shown to substantially decrease indinavir concentrations (see CLINICAL PHARMACOLOGY, *Drug Interactions*) and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

PRECAUTIONS

General

Indirect hyperbilirubinemia has occurred frequently during treatment with CRIXIVAN and has infrequently been associated with increases in serum transaminases (see also ADVERSE REACTIONS, *Clinical Trials* and *Post-Marketing Experience*). It is not known whether CRIXIVAN will exacerbate the physiologic hyperbilirubinemia seen in neonates. (See *Pregnancy*.)

Tubulointerstitial Nephritis

Reports of tubulointerstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leukocyturia (>100 cells/ high power field). Patients with asymptomatic severe leukocyturia should be followed closely and monitored frequently with urinalyses. Further diagnostic evaluation may be warranted, and discontinuation of CRIXIVAN should be considered in all patients with severe leukocyturia.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including CRIXIVAN. During the initial phase of treatment, patients responding to antiretroviral therapy whose immune system responds to CART may develop an inflammatory response to indolent or residual opportunistic infections (such as MAI, CMV, PCP, or TB), which may necessitate further evaluation and treatment.

Coexisting Conditions

Patients with hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (See ADVERSE REACTIONS, *Post-Marketing Experience*.)

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN (see DOSAGE AND ADMINISTRATION).

Patients with renal insufficiency: Patients with renal insufficiency have not been studied.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label. **ALERT: Find out about medicines that should NOT be taken with CRIXIVAN.** A Patient Package Insert (PPI) for CRIXIVAN is available for patient information.

CRIXIVAN is not a cure for HIV infection and patients may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of CRIXIVAN are unknown at this time. CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using CRIXIVAN and should not modify or discontinue treatment without first consulting the physician. Therefore, if a dose is missed, patients should take the next dose at the regularly scheduled time and should not double this dose. Therapy with CRIXIVAN should be initiated and maintained at the recommended dosage.

CRIXIVAN may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar (see CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption* and DOSAGE AND ADMINISTRATION). Ingestion of CRIXIVAN with a meal high in calories, fat, and protein reduces the absorption of indinavir.

Patients receiving a phosphodiesterase type 5 (PDE5) inhibitor (sildenafil, tadalafil, or vardenafil) should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctors.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

CRIXIVAN Capsules are sensitive to moisture. Patients should be informed that CRIXIVAN should be stored and used in the original container and the desiccant should remain in the bottle.

Drug Interactions

Indinavir is an inhibitor of the cytochrome P450 isoform CYP3A4. Coadministration of CRIXIVAN and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see CONTRAINDICATIONS and WARNINGS).

Indinavir is metabolized by CYP3A4. Drugs that induce CYP3A4 activity would be expected to increase the clearance of indinavir, resulting in lowered plasma concentrations of indinavir. Coadministration of CRIXIVAN and other drugs that inhibit CYP3A4 may decrease the clearance of indinavir and may result in increased plasma concentrations of indinavir.

Table 8
Drugs That Should Not Be Coadministered with CRIXIVAN

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Sedative/hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions

	such as prolonged or increased sedation or respiratory depression.
GI motility agents: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors or other coadministered antiretroviral agents.
HMG-CoA Reductase inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.

Protease inhibitor: atazanavir	Both CRIXIVAN and atazanavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of CRIXIVAN and atazanavir is not recommended.

Table 9
Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See also CLINICAL PHARMACOLOGY for magnitude of interaction, WARNINGS and DOSAGE AND ADMINISTRATION.)

Drug Name	Effect	Clinical Comment
HIV Antiviral Agents		
Delavirdine	↑ indinavir concentration	Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when taking delavirdine 400 mg three times a day.
Didanosine		Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach.
Efavirenz	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Nelfinavir	↑ indinavir concentration	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Nevirapine	↓ indinavir concentration	Indinavir concentrations may be decreased in the presence of nevirapine. The appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Ritonavir	↑ indinavir concentration ↑ ritonavir concentration	The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Preliminary clinical data suggest that the incidence of nephrolithiasis is higher in patients receiving indinavir in combination with ritonavir than those receiving CRIXIVAN 800 mg q8h.
Saquinavir	↑ saquinavir concentration	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic) and quinidine	↑ antiarrhythmic agents concentration	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with CRIXIVAN.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ indinavir concentration	Use with caution. CRIXIVAN may not be effective due to decreased indinavir concentrations in patients taking these agents concomitantly.
Calcium Channel	↑ dihydropyridine calcium channel	Caution is warranted and clinical monitoring of patients is recommended.

Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	blockers concentration	
Clarithromycin	↑ clarithromycin concentration ↑ indinavir concentration	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.
HMG-CoA Reductase Inhibitor: atorvastatin	↑ atorvastatin concentration	Use lowest possible dose of atorvastatin with careful monitoring, or consider HMG-CoA reductase inhibitors that are not primarily metabolized by CYP3A4, such as pravastatin, fluvastatin, or rosuvastatin in combination with CRIXIVAN.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressant agents concentration	Plasma concentrations may be increased by CRIXIVAN.
Itraconazole	↑ indinavir concentration	Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering itraconazole concurrently.
Ketoconazole	↑ indinavir concentration	Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.
Rifabutin	↓ indinavir concentration ↑ rifabutin concentration	Dose reduction of rifabutin to half the standard dose and a dose increase of CRIXIVAN to 1000 mg (three 333-mg capsules) every 8 hours are recommended when rifabutin and CRIXIVAN are coadministered.
Sildenafil	↑ sildenafil concentration	Sildenafil dose should not exceed a maximum of 25 mg in a 48-hour period in patients receiving concomitant indinavir therapy.
Tadalafil	↑ tadalafil concentration	Tadalafil dose should not exceed a maximum of 10 mg in a 72-hour period in patients receiving concomitant indinavir therapy.
Vardenafil	↑ vardenafil concentration	Vardenafil dose should not exceed a maximum of 2.5 mg in a 24-hour period in patients receiving concomitant indinavir therapy.
Note: ↑ = increase; ↓ = decrease		

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest dose tested in rats was 640 mg/kg/day; at this dose a statistically significant increased incidence of thyroid adenomas was seen only in male rats. At that dose, daily systemic exposure in rats was approximately 1.3 times higher than daily systemic exposure in humans. No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, *in vitro* and *in vivo* chromosomal aberration studies, and *in vitro* mammalian cell mutagenesis assays. No treatment-related effects on mating, fertility, or embryo survival were seen in female rats and

no treatment-related effects on mating performance were seen in male rats at doses providing systemic exposure comparable to or slightly higher than that with the clinical dose. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

Pregnancy

Pregnancy Category C: Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal plasma drug levels were approximately 10 to 15% and 10 to 20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1 to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with CRIXIVAN (see PRECAUTIONS and ADVERSE REACTIONS). It is unknown whether CRIXIVAN administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant women. CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to CRIXIVAN, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether CRIXIVAN is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving CRIXIVAN. This is consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m^2 every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were <u>not</u> comparable to profiles previously observed in adults receiving the recommended dose (see CLINICAL PHARMACOLOGY, *Pediatric*). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see WARNINGS, *Nephrolithiasis/Urolithiasis*). Physicians considering the use of indinavir in pediatric patients

without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

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.

ADVERSE REACTIONS

Clinical Trials in Adults

Nephrolithiasis/urolithiasis, including flank pain with or without hematuria (including microscopic hematuria), has been reported in approximately 12.4% (301/2429; range across individual trials: 4.7% to 34.4%) of patients receiving CRIXIVAN at the recommended dose in clinical trials with a median follow-up of 47 weeks (range: 1 day to 242 weeks; 2238 patient-years follow-up). The cumulative frequency of nephrolithiasis events increases with duration of exposure to CRIXIVAN; however, the risk over time remains relatively constant. Of the patients treated with CRIXIVAN who developed nephrolithiasis/urolithiasis in clinical trials during the double-blind phase, 2.8% (7/246) were reported to develop hydronephrosis and 4.5% (11/246) underwent stent placement. Following the acute episode, 4.9% (12/246) of patients discontinued therapy. (See WARNINGS and DOSAGE AND ADMINISTRATION, *Nephrolithiasis/Urolithiasis*.)

Asymptomatic hyperbilirubinemia (total bilirubin ≥2.5 mg/dL), reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with CRIXIVAN. In <1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis/urolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses ≤2.4 g/day.

Clinical adverse experiences reported in ≥2% of patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 10.

Table 10
Clinical Adverse Experiences Reported in ≥2% of Patients

	Study 028 Considered Drug-Related and of Moderate or Severe Intensity			Study ACTG 320 of Unknown Drug Relationship and of Severe or Life-threatening Intensity	
Adverse Experience	CRIXIVAN Percent (n=332)	CRIXIVAN plus Zidovudine Percent (n=332)	Zidovudine Percent (n=332)	CRIXIVAN plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
Body as a Whole					
Abdominal pain	16.6	16.0	12.0	1.9	0.7
Asthenia/fatigue	2.1	4.2	3.6	2.4	4.5
Fever	1.5	1.5	2.1	3.8	3.0
Malaise	2.1	2.7	1.8	0	0
Digestive System					
Nausea	11.7	31.9	19.6	2.8	1.4
Diarrhea	3.3	3.0	2.4	0.9	1.2
Vomiting	8.4	17.8	9.0	1.4	1.4
Acid regurgitation	2.7	5.4	1.8	0.4	0
Anorexia	2.7	5.4	3.0	0.5	0.2
Appetite increase	2.1	1.5	1.2	0	0
Dyspepsia	1.5	2.7	0.9	0	0
Jaundice	1.5	2.1	0.3	0	0
Hemic and Lymphatic System					
Anemia	0.6	1.2	2.1	2.4	3.5
Musculoskeletal System					
Back pain	8.4	4.5	1.5	0.9	0.7
Nervous System/Psychiatric					
Headache	5.4	9.6	6.0	2.4	2.8
Dizziness	3.0	3.9	0.9	0.5	0.7
Somnolence	2.4	3.3	3.3	0	0
Skin and Skin Appendage					
Pruritus	4.2	2.4	1.8	0.5	0
Rash	1.2	0.6	2.4	1.1	0.5
Respiratory System					
Cough	1.5	0.3	0.6	1.6	1.0
Difficulty breathing/ dyspnea/shortness of breath	0	0.6	0.3	1.8	1.0

Urogenital System					
Nephrolithiasis/urolit	8.7	7.8	2.1	2.6	0.3
hiasis*	1.5	2.4	0.3	0.4	0.2
Dysuria					
Special Senses					
Taste perversion	2.7	8.4	1.2	0.2	0

*Including renal colic, and flank pain with and without hematuria

In Phase I and II controlled trials, the following adverse events were reported significantly more frequently by those randomized to the arms containing CRIXIVAN than by those randomized to nucleoside analogues: rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Selected laboratory abnormalities of severe or life-threatening intensity reported in patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 11.

Table 11
Selected Laboratory Abnormalities of Severe or Life-threatening Intensity
Reported in Studies 028 and ACTG 320

	Study 028			Study ACTG 320	
	CRIXIVAN Percent (n=329)	CRIXIVAN plus Zidovudine Percent (n=320)	Zidovudine Percent (n=330)	CRIXIVAN plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
Hematology					
Decreased hemoglobin <7.0 g/dL	0.6	0.9	3.3	2.4	3.5
Decreased platelet count <50 THS/mm³	0.9	0.9	1.8	0.2	0.9
Decreased neutrophils <0.75 THS/mm³	2.4	2.2	6.7	5.1	14.6
Blood chemistry					
Increased ALT >500% ULN*	4.9	4.1	3.0	2.6	2.6
Increased AST >500% ULN	3.7	2.8	2.7	3.3	2.8
Total serum bilirubin >250% ULN	11.9	9.7	0.6	6.1	1.4
Increased serum amylase >200% ULN	2.1	1.9	1.8	0.9	0.3
Increased glucose >250 mg/dL	0.9	0.9	0.6	1.6	1.9
Increased creatinine >300% ULN	0	0	0.6	0.2	0

*Upper limit of the normal range.

Post-Marketing Experience

Body As A Whole: redistribution/accumulation of body fat (see PRECAUTIONS, *Fat Redistribution*).

Cardiovascular System: cardiovascular disorders including myocardial infarction and angina pectoris; cerebrovascular disorder.

Digestive System: liver function abnormalities; hepatitis including reports of hepatic failure (see WARNINGS); pancreatitis; jaundice; abdominal distention; dyspepsia.

Hematologic: increased spontaneous bleeding in patients with hemophilia (see PRECAUTIONS); acute hemolytic anemia (see WARNINGS).

Endocrine/Metabolic: new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia (see WARNINGS).

Hypersensitivity: anaphylactoid reactions; urticaria; vasculitis.

Musculoskeletal System: arthralgia.

Nervous System/Psychiatric: oral paresthesia; depression.

Skin and Skin Appendage: rash including erythema multiforme and Stevens-Johnson syndrome; hyperpigmentation; alopecia; ingrown toenails and/or paronychia; pruritus.

Urogenital System: nephrolithiasis/urolithiasis; in some cases resulting in renal insufficiency or acute renal failure, pyelonephritis with or without bacteremia (see WARNINGS); interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of CRIXIVAN; leukocyturia; (see PRECAUTIONS), crystalluria; dysuria.

Laboratory Abnormalities

Increased serum triglycerides; increased serum cholesterol.

OVERDOSAGE

There have been more than 60 reports of acute or chronic human overdosage (up to 23 times the recommended total daily dose of 2400 mg) with CRIXIVAN. The most commonly reported symptoms were renal (e.g., nephrolithiasis/urolithiasis, flank pain, hematuria) and gastrointestinal (e.g., nausea, vomiting, diarrhea).

It is not known whether CRIXIVAN is dialyzable by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dosage of CRIXIVAN is 800 mg (usually **two** 400-mg capsules) orally every 8 hours.

CRIXIVAN must be taken at intervals of 8 hours. For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar. (See CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption.*)

To ensure adequate hydration, it is recommended that adults drink at least 1.5 liters (approximately 48 ounces) of liquids during the course of 24 hours.

Concomitant Therapy (See CLINICAL PHARMACOLOGY, *Drug Interactions*, and/or PRECAUTIONS, *Drug Interactions.*)

Delavirdine

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day.

Didanosine

If indinavir and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach (consult the manufacturer's product circular for didanosine).

Itraconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently.

Ketoconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering ketoconazole concurrently.

Rifabutin

Dose reduction of rifabutin to half the standard dose (consult the manufacturer's product circular for rifabutin) and a dose increase of CRIXIVAN to 1000 mg (**three** 333-mg capsules) every 8 hours are recommended when rifabutin and CRIXIVAN are coadministered.

Hepatic Insufficiency

The dosage of CRIXIVAN should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

Nephrolithiasis/Urolithiasis

In addition to adequate hydration, medical management in patients who experience nephrolithiasis/urolithiasis may include temporary interruption (e.g., 1 to 3 days) or discontinuation of therapy.

HOW SUPPLIED

CRIXIVAN Capsules are supplied as follows:

No. 3755 — 100 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 100 mg"** in green. Available as:

NDC 0006-0570-62 unit-of-use bottles of 180 (with desiccant).

No. 3756 — 200 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 200 mg"** in blue. Available as:

NDC 0006-0571-43 unit-of-use bottles of 360 (with desiccant).

No. 3802 — 333 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 333 mg"** in red and a radial red band on the body. Available as:

NDC 0006-0574-65 unit-of-use bottles of 135 (with desiccant).

No. 3758 — 400 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 400 mg"** in green. Available as:

NDC 0006-0573-42 unit-dose packages of 42
NDC 0006-0573-40 unit-of-use bottles of 120 (with desiccant)
NDC 0006-0573-62 unit-of-use bottles of 180 (with desiccant)
NDC 0006-0573-54 unit-of-use bottles of 90 (with desiccant)
NDC 0006-0573-18 unit-of-use bottles of 18 (with desiccant).

Storage

Bottles: Store in a tightly-closed container at room temperature, 15-30°C (59-86°F). Protect from moisture.

CRIXIVAN Capsules are sensitive to moisture. CRIXIVAN should be dispensed and stored in the original container. The desiccant should remain in the original bottle.

Unit-Dose Packages: Store at room temperature, 15-30°C (59-86°F). Protect from moisture.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued ~~January 2002~~
Printed in USA

CRIXIVAN®* (indinavir sulfate) Capsules

Patient Information about

CRIXIVAN (KRIK-sih-van)

for HIV (Human Immunodeficiency Virus) Infection

Generic name: indinavir (in-DIH-nuh-veer) sulfate

ALERT: Find out about medicines that should NOT be taken with CRIXIVAN. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH CRIXIVAN".

Please read this information before you start taking CRIXIVAN. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss CRIXIVAN when you start taking your medication and at regular checkups. You should remain under a doctor's care when using CRIXIVAN and should not change or stop treatment without first talking with your doctor.

What is CRIXIVAN?

CRIXIVAN is an oral capsule used for the treatment of HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (acquired immune deficiency syndrome). CRIXIVAN is a type of HIV drug called a protease (PRO-tee-ase) inhibitor.

How does CRIXIVAN work?

CRIXIVAN is a protease inhibitor that fights HIV. CRIXIVAN can help reduce your chances of getting illnesses associated with HIV. CRIXIVAN can also help lower the amount of HIV in your body (called "viral load") and raise your CD4 (T) cell count. CRIXIVAN may not have these effects in all patients.

CRIXIVAN is usually prescribed with other anti-HIV drugs such as ZDV (also called AZT), 3TC, ddI, ddC, or d4T. CRIXIVAN works differently from these other anti-HIV drugs. Talk with your doctor about how you should take CRIXIVAN.

How should I take CRIXIVAN?

There are six important things you must do to help you benefit from CRIXIVAN:

1. **Take CRIXIVAN capsules every day as prescribed by your doctor.** Continue taking CRIXIVAN unless your doctor tells you to stop. Take the exact amount of CRIXIVAN that your doctor tells you to take, right from the very start. To help make sure you will benefit from CRIXIVAN, you must not skip doses or take "drug holidays". If you don't take CRIXIVAN as prescribed, the activity of CRIXIVAN may be reduced (due to resistance).

2. **Take CRIXIVAN capsules every 8 hours around the clock, *every day*.** It may be easier to remember to take CRIXIVAN if you take it at the same time every day. If you have questions about when to take CRIXIVAN, your doctor or health care provider can help you decide what schedule works for you.

---

3. **If you miss a dose by more than 2 hours, wait and then take the next dose at the regularly scheduled time.** However, if you miss a dose by less than 2 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of CRIXIVAN at any one time.

4. **Take CRIXIVAN with water.** You can also take CRIXIVAN with other beverages such as skim or non-fat milk, juice, coffee, or tea.

5. **Ideally, take each dose of CRIXIVAN without food but with water at least one hour before or two hours after a meal.** Or you can take CRIXIVAN with a light meal. Examples of light meals include:
   dry toast with jelly, juice, and coffee (with skim or non-fat milk and sugar if you want)
   cornflakes with skim or non-fat milk and sugar
   Do not take CRIXIVAN at the same time as any meals that are high in calories, fat, and protein (for example — a bacon and egg breakfast). When taken at the same time as CRIXIVAN, these foods can interfere with CRIXIVAN being absorbed into your bloodstream and may lessen its effect.

6. **It is critical to drink plenty of fluids while taking CRIXIVAN.** Adults should drink at least six 8-ounce glasses of liquids (preferably water) throughout the day, every day. Your health care provider will give you further instructions on the amount of fluid that you should drink. **CRIXIVAN can cause kidney stones.** Having enough fluids in your body should help reduce the chances of forming a kidney stone. Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Does CRIXIVAN cure HIV or AIDS?

CRIXIVAN is not a cure for HIV or AIDS. People taking CRIXIVAN may still develop infections or other conditions associated with HIV. Because of this, it is very important for you to remain under the care of a doctor. Although CRIXIVAN is not a cure for HIV or AIDS, CRIXIVAN can help reduce your chances of getting illnesses, including death, associated with HIV. CRIXIVAN may not have these effects in all patients.

Does CRIXIVAN reduce the risk of passing HIV to others?

CRIXIVAN has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination.

Who should not take CRIXIVAN?

Do not take CRIXIVAN if you have had a serious allergic reaction to CRIXIVAN or any of its components.

What other medical problems or conditions should I discuss with my doctor?

Talk to your doctor if:

- You are pregnant or if you become pregnant while you are taking CRIXIVAN. We do not yet know how CRIXIVAN affects pregnant women or their developing babies.
- You are breast-feeding. You should stop breast-feeding if you are taking CRIXIVAN.

Also talk to your doctor if you have:

- Problems with your liver, especially if you have mild or moderate liver disease caused by cirrhosis.
- Problems with your kidneys.
- Diabetes
- Hemophilia
- High cholesterol and you are taking cholesterol-lowering medicines called "statins".

Tell your doctor about any medicines you are taking or plan to take, including non-prescription medicines, herbal products including St. John's wort (*Hypericum perforatum*), or dietary supplements.

Can CRIXIVAN be taken with other medications?**

MEDICINES YOU SHOULD NOT TAKE WITH CRIXIVAN

VERSED®
(midazolam)
ORAP®
(pimozide)
PROPULSID®
(cisapride)
CORDARONE®
(amiodarone)
HISMANAL®
(astemizole)
HALCION®
(triazolam)
Ergot medications
(e.g., Wigraine®, Cafergot®, D.H.E. 45®, Migranal®, Ergotrate®, and Methergine®)

Taking CRIXIVAN with the above medications could result in serious or life-threatening problems (such as irregular heartbeat or excessive sleepiness).

In addition, you should not take CRIXIVAN with the following:

Rifampin, known as RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE®.

It is not recommended to take CRIXIVAN with the cholesterol-lowering drugs MEVACOR* (lovastatin) or ZOCOR* (simvastatin) because of possible drug interactions. There is also an increased risk of drug interactions between CRIXIVAN and LIPITOR® (atorvastatin); talk to your doctor before you take any of these cholesterol-reducing drugs with CRIXIVAN.

Taking CRIXIVAN with REYATAZ® (atazanavir) is not recommended because they can both sometimes cause increased levels of bilirubin in the blood.

Taking CRIXIVAN with St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort is not recommended. Taking St. John's wort has been shown to decrease CRIXIVAN levels and may lead to increased viral load and possible resistance to CRIXIVAN or cross resistance to other antiretroviral drugs.

Before you take VIAGRA® (sildenafil), CIALIS® (tadalafil), or LEVITRA® (vardenafil) with CRIXIVAN, talk to your doctor about possible drug interactions and side effects. If you take any of these medicines together with CRIXIVAN, you may be at increased risk of side effects such as low blood pressure, visual changes, and penile erection lasting more than 4 hours, which have been associated with sildenafil, tadalafil, and vardenafil. If an erection lasts longer than 4 hours, you should seek immediate medical assistance to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

MEDICINES YOU CAN TAKE WITH CRIXIVAN

RETROVIR®
(zidovudine, ZDV
also called AZT)

EPIVIR™
(lamivudine, 3TC)

ZERIT®
(stavudine, d4T)

isoniazid
(INH)

BACTRIM®/SEPTRA®
(trimethoprim/sulfamethoxazole)

DIFLUCAN®
(fluconazole)

BIAXIN®
(clarithromycin)

ORTHO-NOVUM 1/35®
(oral contraceptive)

TAGAMET®
(cimetidine)

Methadone

CRESTOR®
(rosuvastatin)

VIDEX® (didanosine, ddI) — If you take CRIXIVAN with VIDEX, take them at least one hour apart.

MYCOBUTIN® (rifabutin) — If you take CRIXIVAN with MYCOBUTIN, your doctor may adjust both the dose of MYCOBUTIN and the dose of CRIXIVAN.

NIZORAL® (ketoconazole) — If you take CRIXIVAN with NIZORAL, your doctor may adjust the dose of CRIXIVAN.

RESCRIPTOR® (delavirdine) — If you take CRIXIVAN with RESCRIPTOR, your doctor may adjust the dose of CRIXIVAN.

SPORANOX® (itraconazole) — If you take CRIXIVAN with SPORANOX, your doctor may adjust the dose of CRIXIVAN.

SUSTIVA™ (efavirenz) — If you take CRIXIVAN with SUSTIVA, your doctor may adjust the dose of CRIXIVAN.

Talk to your doctor about any medications you are taking.

Calcium Channel Blockers: Tell your doctor if you are taking calcium channel blockers (e.g., amlodipine, felodipine).

Antiarrhythmics: Tell your doctor if you are taking antiarrhythmics (e.g., quinidine).

Anticonvulsants: Tell your doctor if you are taking anticonvulsants (e.g., phenobarbital, phenytoin, or carbamazepine).

Steroids: Tell your doctor if you are taking steroids (e.g., dexamethasone).

What are the possible side effects of CRIXIVAN?

Like all prescription drugs, CRIXIVAN can cause side effects. The following is **not** a complete list of side effects reported with CRIXIVAN when taken either alone or with other anti-HIV drugs. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Some patients treated with CRIXIVAN developed kidney stones. In some of these patients this led to more severe kidney problems, including kidney failure or inflammation of the kidneys or kidney infection which sometimes spread to the blood. Drinking at least six 8-ounce glasses of liquids (preferably water) each day should help reduce the chances of forming a kidney stone (see **How should I take CRIXIVAN?).** Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Some patients treated with CRIXIVAN have had rapid breakdown of red blood cells (hemolytic anemia) which in some cases was severe or resulted in death.

Some patients treated with CRIXIVAN have had liver problems including liver failure and death. Some patients had other illnesses or were taking other drugs. It is uncertain if CRIXIVAN caused these liver problems.

Diabetes and high blood sugar (hyperglycemia) have occurred in patients taking protease inhibitors. In some of these patients, this led to ketoacidosis, a serious condition caused by poorly controlled blood sugar. Some patients had diabetes before starting protease inhibitors, others did not. Some patients required adjustments to their diabetes medication. Others needed new diabetes medication.

In some patients with hemophilia, increased bleeding has been reported.

Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with some of the cholesterol-lowering medicines called "statins". Call your doctor if you develop severe muscle pain or weakness.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from opportunistic infections may occur when combination antiretroviral treatment is started.

Clinical Studies

Increases in bilirubin (one laboratory test of liver function) have been reported in approximately 14% of patients. Usually, this finding has not been associated with liver problems. However, on rare occasions, a person may develop yellowing of the skin and/or eyes.

Side effects occurring in 2% or more of patients included: abdominal pain, fatigue or weakness, low red blood cell count, flank pain, painful urination, feeling unwell, nausea, upset stomach, diarrhea, vomiting, acid regurgitation, increased or decreased appetite, back pain, headache, dizziness, taste changes, rash, itchy skin, yellowing of the skin and/or eyes, upper respiratory infection, dry skin, and sore throat.

Swollen kidneys due to blocked urine flow occurred rarely.

Marketing Experience

Other side effects reported since CRIXIVAN has been marketed include: allergic reactions; severe skin reactions; yellowing of the skin and/or eyes; heart problems including heart attack; stroke; abdominal swelling; indigestion; inflammation of the kidneys; inflammation of the pancreas; joint pain; depression; itching; hives; change in skin color; hair loss; ingrown toenails with or without infection; crystals in the urine; painful urination; numbness of the mouth and increased cholesterol.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

How should I store CRIXIVAN capsules?

- Keep CRIXIVAN capsules in the bottle they came in and at room temperature (59°-86°F).
- Keep CRIXIVAN capsules dry by leaving the small desiccant in the bottle. Keep the bottle closed.

This medication was prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep CRIXIVAN and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about CRIXIVAN. If you have any questions or concerns about either CRIXIVAN or HIV, talk to your doctor.

**The brands listed are the registered trademarks of their respective owners and are not trademarks of Merck & Co., Inc.

Issued ~~January 2002~~

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

MEDICAL REVIEW

Medical Officer's Review
Supplemental NDA
20-685 / S-047

Date of submission: June 9, 2000
Date received: June 12, 2000
Date assigned: June 14, 2000
Draft MOR completed: April 4, 2001
MOR completed: April 25, 2001

Applicant:	Merck Research Laboratories Sumneytown Pike West Point, PA 19486
Drug Class:	HIV-1 Protease Inhibitor
Drug Name	Generic: MK-0639, indinavir sulfate Trade: Crixivan™
Dosage and Administration:	100, 200, 333 and 400 mg capsule Given orally twice daily
Indication:	Treatment of HIV infection in adults
Reason for submission:	Labeling supplement – 047
Background:	The original NDA was submitted on January 31, 1996 and Crixivan™ received accelerated approval on March 31, 1996. Traditional approval was February 6, 1998.
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-041, S-042, S-043, S-045
Related NDAs and INDs:	IND
Amendments:	April 11, 2001

TABLE OF CONTENTS

I. Resume

The submitted material consists of a one volume study report for Merck Study 078 and a CD containing the submission in an electronic format. Merck Study 078 was a Phase I pharmacokinetics and safety study of four twice daily combinations of Crixivan™ and ritonavir in 73 healthy adult volunteers. The sponsor has proposed changes in the Clinical Pharmacology, *Drug Interactions* and Precautions, *Drug Interactions* sections of the Crixivan package insert to reflect the results of this study.

II. Merck Study 078

Merck 078, "A double-blind, placebo-controlled, parallel-group study to investigate the tolerability and pharmacokinetics of multiple doses of Crixivan in combination with ritonavir in healthy volunteers," studied four different combinations of indinavir and ritonavir. The single-center study, which enrolled healthy adult volunteers, was initiated in June 1998 and completed in August 1998.

A. Study Design

Merck study 078 was a single-center, double-blind, placebo-controlled, parallel-group study designed to examine the tolerability and pharmacokinetics of indinavir in combination with ritonavir. The primary objectives of this study were to evaluate the tolerability of different combinations of indinavir and ritonavir compared to ritonavir alone and to evaluate indinavir and ritonavir pharmacokinetic parameters (AUC, C_{max}, and C_{12h}) obtained at steady state with the study drug regimens. The secondary objectives were to compare the effect of a high fat and a low fat meal on indinavir and on ritonavir pharmacokinetic measurements and to estimate the C_{24h} concentrations of indinavir and ritonavir after a high fat meal.

Men and women from 18 to 45 years of age who were HIV seronegative and within 20% of their ideal body weight were eligible for this study. The study was designed to enroll approximately 70 subjects (12 randomized to each of four different study arms of indinavir and ritonavir in combination, six randomized to each of the control arms containing ritonavir, and four randomized to a placebo arm) with the goal of obtaining pharmacokinetic results from 59 subjects. The study arms are shown in Table 1 below.

Table 1: Merck 078 Study Regimens

Study Arms		
Group	**Indinavir Dosage**	**Ritonavir Dosage**
A	800 q 12 hr	100 q 12 hr
B	800 q 12 hr	200 q 12 hr
C	800 q 12 hr	400 q 12 hr
D	400 q 12 hr	400 q 12 hr
Control Arms		
Group	**Indinavir Dosage**	**Ritonavir Dosage**
E	Placebo	100 q 12 hr
F	Placebo	200 q 12 hr
G	Placebo	400 q 12 hr
H	Placebo	Placebo

Source: NDA 20-685, S-047 submission, page 310.

Subjects in each treatment arm received indinavir, ritonavir, and / or placebo every 12 hours and were instructed to take the study drugs with a low fat meal or snack. Pharmacokinetic parameters were measured predose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose on day 14 after a low fat breakfast and on day 15 after a high fat breakfast. Subjects stopped their study drugs after the day 15 morning dose. Additional pharmacokinetic sampling was obtained 16 and 24 hours after the day 15 morning dose of study drug. Urine samples for indinavir concentrations were collected during six separate time periods after dosing: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, and 10 to 12 hours. Pharmacokinetic parameters were evaluated with AUC_{0-12}, C_{max}, T_{max}, and C_{12h} measurements; statistical analysis of the pharmacokinetic measurements included arithmetic means, standard deviations, geometric means, and geometric mean ratios with the corresponding 90% confidence intervals. Safety data were collected as a tabulation of adverse events. Subjects were evaluated at a prestudy screening two weeks before starting study drug, before the first dose of study drug, on days 4, 9, 14, 15 and 16, and at a post study visit two weeks after completing the study.

B. Merck Study 078 Results

1. Study Population and Subject Accounting

Seventy-three healthy adult volunteers were enrolled in Merck 078. The majority were female (60%) and white (62%). The median age was 27 years with a range from 18 to 45 years. The distribution by gender and race varied across the different study arms, but the distribution by age was similar among the different study arms.

A total of 20 subjects (27%) of the 73 who enrolled in the study subsequently discontinued the study prematurely. Ten (14%) discontinued due to a clinical adverse event, no subjects discontinued due to a laboratory event. Eight subjects withdrew from the study with no reason provided, one subject was lost to follow-up, and one subject discontinued for "other" reasons. On review of the Case Report Forms for these ten subjects, nine subjects discontinued the study after reporting at least one adverse event.

The distribution of subjects discontinuing the study across the different study arms is shown in Table 2.

Table 2: Subject Discontinuations in Merck 078

Treatment Regimen*	No. of Patients Enrolled	No. of Patients Discontinuing	No. of Patients Discontinuing due to an AE
IDV 800/RTV100	13	3	1
IDV 800/RTV200	12	4	3
IDV 800/RTV400	13	4	2
IDV 400/RTV400	13	3	3
PBO/RTV100	6	3	0
PBO/RTV200	6	1	0
PBO/RTV400	6	1	1
PBO/PBO	4	1	0
Total	**73**	**20**	**10**

*IDV = indinavir, RTV = ritonavir, and PBO = placebo
Source: NDA 20-685, S-047, page 40, Table 7.

A total of 52 subjects had pharmacokinetic measurements obtained on day 14 and 50 on day 15; one subject receiving 800 mg of indinavir and 200 mg of ritonavir twice daily and one subject receiving placebo and 100 mg of ritonavir had day 14 measurements but not day 15 measurements. The reasons that these two subjects did not complete the study were not provided.

2. Pharmacokinetic Analysis

Pharmacokinetic measurements were obtained for 52 subjects on day 14 after a low-fat meal. Indinavir pharmacokinetic parameters observed after each combination that included 800 mg of indinavir were compared to the those noted with combinations that contained 400 mg of indinavir and with those seen with the standard indinavir regimen of 800 mg every eight hours. The arithmetic means of indinavir pharmacokinetic parameters for the different treatment arms are shown in Table 3 below.

Table 3: Arithmetic Means of Indinavir Pharmacokinetic Measurements after the Coadministration of Indinavir and Ritonavir with a Low Fat Meal on Day 14

Indinavir Measurement	Indinavir / Ritonavir Doses (mg given every 12 hours)				Indinavir
	800/100	**800/200**	**800/400**	**400/400**	**800 q8hr**
$AUC_{0\text{-}12hr}$ (nM•hr)	119,056	159,499	139,090	72,727	28,000
C_{max} (nM)	19,168	21,584	18,049	11,668	11,000
C_{12hr}	2,617	5,950	5,913	2,599	211*

*The Cmin value after the indinavir q8hr regimen was measured 8 hours after dosing.
Source: NDA 20-685, S-047, page 51, Table 9 and page 287.

As shown in Table 3, the indinavir AUC, peak, and trough values were increased when indinavir was given every 12 hours in combination with ritonavir as compared to the AUC, peak, and trough seen in previous studies of indinavir given alone every eight hours. When pharmacokinetic measurements obtained with drug combinations that included 800 mg of indinavir were compared to those seen with indinavir 400 mg / ritonavir 400 mg, the indinavir AUC, peak, and trough were higher with combinations containing 800 mg of indinavir. These results were confirmed when the pharmacokinetic measurements were expressed as geometric means. The geometric mean of each indinavir pharmacokinetic parameter (AUC, C_{max}, and C_{12hr}) obtained with a regimen containing 800 mg of indinavir was higher than the corresponding parameter obtained with the indinavir 400 mg / ritonavir 400 mg regimen. Finally, geometric mean ratios were calculated; for these ratios each indinavir pharmacokinetic measurement was compared to the corresponding parameter for indinavir in the indinavir 400 mg / ritonavir 400 mg regimen. According to the applicant, a geometric mean ratio of 1.5 or greater was meaningful. The geometric mean ratios are shown in Table 4.

Table 4: Geometric Mean Ratios of Indinavir Pharmacokinetic Measurements after the Coadministration of Indinavir and Ritonavir with a Low Fat Meal on Day 14

Indinavir Measurement	**Geometric Mean Ratios**		
	800/100	**800/200**	**800/400**
$AUC_{0\text{-}12hr}$ (nM•hr)	1.66	2.19	1.91
C_{max} (nM)	1.67	1.85	1.57
C_{12hr}	1.07	2.38	2.37

Source: NDA 20-685, S-047, page 56, Table 11.

By the sponsor's criteria, the indinavir AUCs and peaks observed with all three of the regimens containing 800 mg of indinavir were significantly higher than those seen with the indinavir 400 mg / ritonavir 400 mg regimen. However, there was not a meaningful difference between the indinavir trough value observed after the indinavir 800 mg / ritonavir 100 mg compared to the trough noted with the indinavir 400 mg / ritonavir 400 mg regimen. In summary, the indinavir exposure, peak, and trough observed with twice daily combinations of indinavir and ritonavir containing 800 mg of indinavir were higher than those seen in historical controls given indinavir alone 800 mg every eight hours. Indinavir total exposure and peak concentrations with regimens including 800 mg of indinavir were also higher than those noted with the indinavir 400 mg / ritonavir 400 mg regimen. Although indinavir trough values observed with the indinavir 800 mg / ritonavir 200 mg regimen and the indinavir 800 mg / ritonavir 400 mg regimen were significantly higher than the trough observed with the indinavir 400 mg / ritonavir 400 mg regimen, the trough value of the indinavir 800 mg / ritonavir 100 mg regimen was not significantly higher than the trough noted with the indinavir 400 mg / ritonavir 400 mg regimen.

Indinavir pharmacokinetic parameters were also obtained on day 15 after a high fat meal. The geometric and the arithmetic means for the AUC, C_{max} and C_{12hr} were similar after a low fat and after a high fat meal. When the geometric mean ratios were calculated, all

were lower than 1.5. Therefore, high fat meal did not appear to affect the plasma concentrations of indinavir when indinavir was used in combination with ritonavir.

Pharmacokinetic parameters for ritonavir were also determined on both day 14 and day 15 of Merck 078. The arithmetic means for ritonavir pharmacokinetic parameters obtained on day 14 after a low fat meal are shown in Table 5.

Table 5: Arithmetic Means of Ritonavir Pharmacokinetic Measurements after the Coadministration of Indinavir and Ritonavir with a Low Fat Meal on Day 14

Ritonavir Measurement	Treatment Regimen (mg given twice daily)						
	800/100	**PBO/100**	**800/200**	**PBO/200**	**800/400**	**400/400**	**PBO/400**
$AUC_{0\text{-}12hr}$ (nM•hr)	24.1	14.3	57.8	29.3	125.8	129.3	137.3
C_{max} (nM)	3.8	2.3	7.7	6.4	20.2	20.7	21.8
C_{12hr}	0.8	0.5	2.9	0.6	7.1	6.7	6.3

Source: NDA 20-685, S-047, page 71, Table 15

When plasma ritonavir concentrations obtained with indinavir / ritonavir combinations were compared to ritonavir levels obtained with ritonavir alone, the AUC of ritonavir was increased when either 100 mg or 200 mg of ritonavir was given in combination with indinavir, but little difference was seen in the treatment regimens that included 400 mg of ritonavir. Increased ritonavir peak and trough levels were observed with indinavir / ritonavir combinations that included either 100 mg or 200 mg of ritonavir. When geometric mean ratios with the corresponding 90% confidence intervals were calculated, the ritonavir AUC was again higher in the indinavir and ritonavir combinations with either 100 mg or 200 mg of ritonavir. However, there was too much variability in ritonavir C_{max} and C_{12hr} levels, as demonstrated by wide confidence intervals, to distinguish any effect of indinavir on ritonavir peak and trough levels.

Ritonavir pharmacokinetic parameters were also measured on day 15 after a high fat meal, and geometric mean ratios were calculated to compare ritonavir pharmacokinetic parameters obtained after a high fat meal to those obtained after a low fat meal. For regimens containing either 100 mg or 200 mg of ritonavir, the geometric mean ratios were well below 1.00; for the regimens containing 400 mg of ritonavir the geometric mean ratios were closer to 1.0 but were still low. Therefore, indinavir appeared to have no discernable effect on the ritonavir – food interaction.

In conclusion, indinavir plasma concentrations observed with various combinations of indinavir and ritonavir were higher than those seen in historical controls receiving 800 mg every eight hours. In addition, indinavir plasma levels after indinavir / ritonavir combinations containing 800 mg were also higher than those seen after the indinavir 400 mg / ritonavir 400 mg combination. Ritonavir plasma concentrations were increased by the use of ritonavir in combination with indinavir in combinations containing 100 or 200 mg of ritonavir. However, after the dose of ritonavir was increased to 400 mg, no further effect on ritonavir levels was observed with the indinavir / ritonavir combination regimens. Finally, the use of indinavir and ritonavir in combination appeared to result in

similar indinavir pharmacokinetic measurements whether the drugs were administered with a high or low fat meal. In contrast, the use of indinavir and ritonavir in combination had no effect on the ritonavir - food interaction.

3. Safety Analysis

All 73 subjects who enrolled in Merck 078 were included in the safety analysis. There were no serious adverse events or deaths. Ten subjects discontinued Merck 078 because of adverse events; all ten discontinued because of clinical adverse events.

Sixty-five of the 73 subjects (89%) reported at least one clinical adverse event; 64 of these subjects reported at least one clinical adverse event that was described as treatment related. The most common clinical adverse events, defined as events reported in at least 30% of subjects in any treatment group included asthenia / fatigue, abdominal pain, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, paresthesia, hyperesthesia, rash, and taste perversion.

When the incidence of clinical adverse events was compared between the treatment groups, there was an increase in adverse events in the indinavir 800 mg / ritonavir 100 mg, 800 mg / 200 mg, 800 mg / 400 mg, and 400 mg / 400 mg groups compared to the placebo / ritonavir 100 mg which reached statistical significance. An analysis was done to determine any differences between the treatment groups that included 400 mg of ritonavir and the treatment groups containing 100 mg or 200 mg of ritonavir. A higher percentage of subjects receiving 400 mg of ritonavir experienced at least one moderate or severe clinical adverse event, and the total number of moderate or severe clinical adverse events was higher in subjects receiving 400 mg of ritonavir. However, no statistical analysis of this data was provided. When odds ratios were determined, the only odds ratio achieving statistical significance was the comparison of moderate and severe adverse events in subjects receiving indinavir 400 mg / ritonavir 400 mg compared to indinavir 800 mg / ritonavir 100 mg.

Nephrolithiasis and abnormal urinalyses have been reported commonly in patients receiving indinavir.[1] In Merck 078 few subjects reported signs or symptoms related to the urogenital system; two subjects reported dysuria, two hematuria, two urinary frequency, and one subject hydronephrosis. Subject AN0053, a 27 year old black female who was receiving indinavir 800 mg / ritonavir 200 mg developed nephrolithiasis on day 3 with hematuria, back and abdominal pain, dysuria, and hydronephrosis. This subject and nine others were discontinued from the study because of clinical adverse events. There was no statistically significant difference in the incidence of study discontinuation between treatment groups. Each subject's reasons for study discontinuation and treatment group are shown in Table 6.

Table 6: Subjects Discontinuing from Merck 078 Due to Clinical Adverse Events

Age / Sex / Race	Clinical Adverse Events	Treatment Regimen (Indinavir/Ritonavir)
36 yr BF	Chest pain	800/100
27 yr WF	Nausea, vomiting, back pain	800/200
27 yr BF	Nephrolithiasis	800/200
21 yr WF	Vomiting	800/200
25 yr WM	Fatigue, nausea	800/400
36 yr WF	Nausea, vomiting, dyspepsia, tremor	800/400
31 yr WF	Blurred vision	400/400
20 yr BM	Blurred vision, dizziness	400/400
25 yr WF	Headache, rash, paresthesia	400/400
19 yr WF	Nausea, vomiting, fatigue	PBO/400

Source: NDA 20-685, S-047, pages 96-98, Table 26.

Of the 73 subjects included in the safety analysis, 72 had at least one laboratory test performed. There were no serious laboratory adverse events and no discontinuations due to laboratory adverse events. Only two patients experienced a laboratory adverse event; both were described as treatment related. One subject in the indinavir 400 mg / ritonavir 400 mg treatment group had an increase in creatinine phosphokinase to 427.5 U/L, and one subject in the placebo / ritonavir 400 mg group reported a glucose of 48 mg/dL. Any clinically significant laboratory abnormalities were determined using predefined upper and lower limits for each laboratory value. In Merck 078 three subjects experienced clinically significant laboratory abnormalities. Two subjects had an elevation in AST. Both subjects were in the indinavir 400 mg / ritonavir 400 mg treatment group and for both subjects the AST returned to normal levels. A third subject in the indinavir 800 mg / ritonavir 400 mg group had an increase in serum amylase on day 4 that resolved by day 25.

In conclusion, clinical adverse events were commonly reported in subjects participating in Merck 078, and 20% of subjects discontinued the study prematurely. The most frequently reported adverse events were nausea, vomiting, headache, dizziness, diarrhea, paresthesia, and hypesthesia; the most commonly reported adverse events experienced by subjects withdrawing from the study were nausea and / or vomiting. There was no statistically significant difference between the incidence of adverse events among the treatment arms containing both indinavir and ritonavir. In contrast laboratory adverse events occurred only rarely and were of mild severity only.

4. FDA Analysis of Merck 078

Please see Dr. Kumi's review for the FDA pharmacokinetic analysis.

Safety data from Merck 078 were reviewed for all adverse events and for any differences between the study arms containing both indinavir and ritonavir. However, because of the small number of subjects enrolled in each treatment arm, it was difficult to reach any

conclusions about the toxicity of any one treatment regimen or to make comparisons between the treatment arms. The incidence of adverse events in each treatment group were reviewed for any adverse events that occurred at an unusually high rate. Adverse events that were seen in more than 50% of subjects in a treatment arm included nausea (indinavir 800 mg / ritonavir 200 mg arm and indinavir 800 mg / ritonavir 400 mg arm), vomiting (indinavir 800 mg / ritonavir 200 mg arm and indinavir 800 mg / ritonavir 400 mg arm), and abdominal pain (placebo / ritonavir 200 mg arm).

Further analyses were performed to compare indinavir containing treatment arms and treatment arms with ritonavir and indinavir placebo for any evidence of toxicity related to the use of indinavir or related to increased indinavir levels. However, this analysis is limited by the small number of subjects, the lack of a comparator arm studying indinavir 800 mg every eight hours, and the potential impact of increased ritonavir levels. Fifty-one subjects were randomized to study arms containing indinavir and ritonavir and 18 to treatment arms with ritonavir alone. The overall incidence of treatment related adverse events was higher for subjects receiving indinavir and ritonavir (94%) compared to for those receiving ritonavir only (67%). Specific adverse events, which were noted in at least twice as many, subjects receiving indinavir, included nausea, vomiting, dizziness, hypesthesia, and taste perversion.

In the sponsor's analyses, there were more moderate and severe adverse events in subjects on any of the treatment arms containing 400 mg of ritonavir, however, this data was depicted graphically only. When the actual incidence of moderate and severe adverse events was calculated for each treatment group, the results are shown in Table 7.

Table 7: A Comparison of Moderate and Severe Adverse Events By Treatment Arm in Study 078

Treatment Group (Indinavir / Ritonavir)	No of Patients	No of AEs	% of All AEs[1,2]	% of Subjects with AE[1,3]
800 / 400	10	32	35%	77%
800 / 200	8	20	22%	67%
800 / 100	3	7	8%	23%
400 / 400	9	20	22%	69%
PBO / 400	9	20	22%	69%
PBO / 200	2	4	4%	33%
PBO / 100	1	2	2%	17%

1. Includes adverse events of moderate or severe intensity only. 2. Percentage of the total number of AEs for all subjects in Study 078. 3. Percentage of subjects within the treatment group with an AE.
Source: Study 078 Datasets

As seen in Table 7, at least two-thirds of subjects in each treatment arm containing 400 mg of ritonavir experienced moderate or severe adverse events, and the highest percentage of subjects with moderate or severe adverse events was seen in the indinavir 800 mg / ritonavir 400 mg treatment arm. However, two-thirds of the subjects receiving indinavir 800 mg / ritonavir 200 mg also reported moderate or severe adverse events. Although our analysis confirms the high incidence of adverse events in subjects receiving

400 mg of ritonavir, the incidence of adverse events was similar for subjects receiving indinavir 800 mg / ritonavir 200 mg. In summary, it appeared that subjects receiving indinavir 800 mg and ritonavir 100 mg had the lowest incidence of adverse events, but it was difficult to detect any differences in the incidence or type of adverse events between the other combinations of indinavir and ritonavir.

Only two subjects reported a laboratory adverse event in Merck 078. On further analysis of chemistry and hematology laboratory datasets, few abnormalities were noted and the abnormalities were generally minor. A total of 35 subjects had total bilirubin levels greater than the upper limit of normal; 12 subjects had total bilirubin levels over 2 U/L including one subject with a total bilirubin level greater than 4.0 U/L. Twenty-three subjects reported an increased creatinine phosphokinase; six subjects had levels more than twice the upper limit of normal for the laboratory. Fourteen subjects had elevated triglyceride levels including two subjects with triglyceride levels over 500 mg/dL. Finally, 29 subjects experienced a hemoglobin value below the lower limit of normal during the study, but only one value was below 10 gm/dL.

Abnormalities related to the urinary tract were also reviewed because of the high incidence of nephrolithiasis and urinary tract abnormalities that has been reported in HIV-infected adults receiving indinavir.[1] Signs and symptoms related to the urinary tract were reported in seven subjects. Six of these subjects were receiving indinavir; these subjects reported dysuria (2 subjects), hematuria (2), hydronephrosis (1), and urinary frequency (1). One subject, a 27 year old black female receiving indinavir 800 mg / ritonavir 200 mg developed nephrolithiasis on day 3 of the study and reported abdominal and back pain, dysuria, hydronephrosis, and hematuria. A total of 14 subjects receiving indinavir developed a laboratory abnormality related to the urinary tract including hematuria (4 subjects), pyuria (4), proteinuria (5), and crystalluria (5). Two of these subjects also reported abdominal pain but were not diagnosed with nephrolithiasis. This included a 21 year old female receiving indinavir 800 mg / ritonavir 200 mg who developed abdominal pain, hematuria, pyuria, proteinuria, and urinary casts. Interestingly, the one patient who was diagnosed with nephrolithiasis had no abnormalities reported on any of her urinalyses. Only two subjects who were receiving indinavir experienced an increased serum creatinine. One subject on indinavir 800 mg / ritonavir 200 mg had a creatinine of 1.5 mg/dL and developed proteinuria and crystalluria noted on urinalysis. The other subject had a creatinine of 1.6 mg/dL but no other urinary tract abnormalities.

A review of the scientific literature supported our safety concerns. To date more than 30 meeting abstracts describing the clinical use of indinavir and ritonavir in combination have been presented at medical conferences over the last three years.[2] Although much is still not know about the safety of indinavir and ritonavir used in combination, several investigators have reported an increase in adverse experiences associated with the use of such combinations.[3-8] In one of the largest studies of indinavir and ritonavir in combination, the BEST (BID Efficacy and Safety Trial) study, 326 HIV-infected adults on indinavir 800 mg every eight hours were randomized to remain on indinavir alone three times daily or change to open-label indinavir 800 mg and ritonavir 100 mg twice

daily. Both the rate of treatment discontinuation or interruption and the incidence of nephrolithiasis were more than twice as high in the patients receiving twice daily indinavir and ritonavir than in those remaining on indinavir alone.[3] These results are supported by another large study, the NICE study. In this study, 301 of 380 subjects were randomized to change from indinavir 800 mg every eight hours to indinavir 400 mg and ritonavir 400 mg twice daily in combination; 21% of subjects receiving indinavir and ritonavir in combination discontinued the study compared to 15% of those who remained on indinavir alone.[4] A third study of 234 HIV-infected adults on different combinations of indinavir and ritonavir showed an increased incidence of both the total number of adverse events and of nephrolithiasis in subjects receiving indinavir / ritonavir combinations with higher doses of indinavir (600 or 800 mg).[5] In this study, the incidence of nephrolithiasis was higher in patients receiving indinavir 800 mg / ritonavir 100 mg than in patients receiving indinavir 400 mg / ritonavir 400 mg. Difficulties tolerating indinavir and ritonavir combinations and an increased incidence of adverse experiences with these combinations have also been reported in smaller studies.[6-8] In one study of 37 patients receiving indinavir 400 mg / ritonavir 400 mg, 12 patients (26%) discontinued the study because of treatment-related adverse events.[6] Boyd et al reported a higher incidence of nephrolithiasis in HIV-infected adults receiving indinavir 800 mg and ritonavir 100 mg.[7] Finally, in a prospective study of indinavir and ritonavir as salvage therapy for 51 patients who were protease inhibitor experienced, 43% of patients discontinued the study by 12 weeks because of toxicity.[8]

In summary, reports in the scientific literature have raised concerns about the tolerability and safety of antiretroviral regimens containing both indinavir and ritonavir. Although there was an extremely high incidence of adverse events noted in this study, it is difficult to reach any conclusions about the toxicity of any one regimen because of the small number of patients in each treatment arm. More studies are needed to identify the optimal regimen of the combination of indinavir and ritonavir.

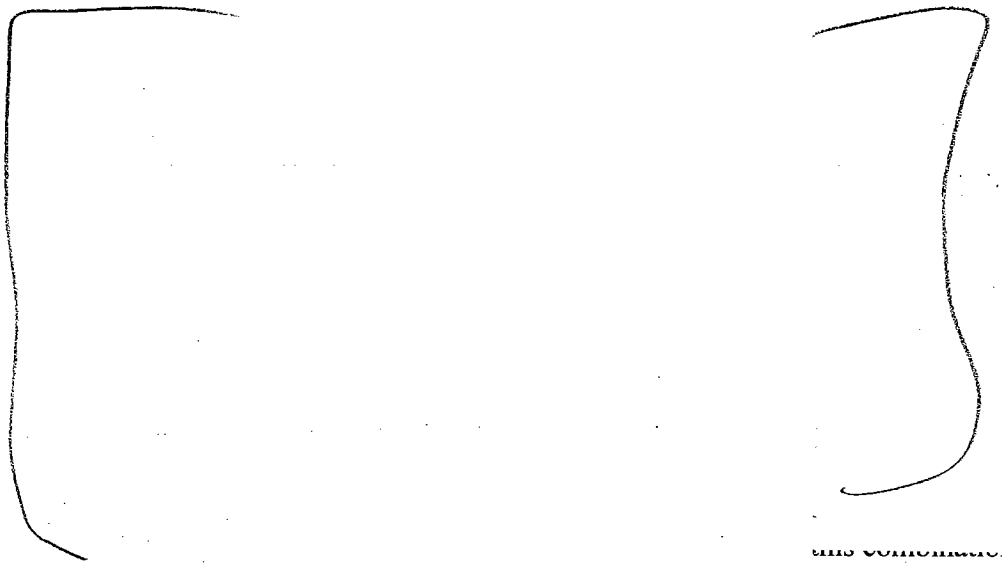
C. Summary

This study demonstrated that indinavir exposure, peak, and trough were significantly increased when indinavir was given to healthy adult volunteers in a twice daily combination with ritonavir compared to indinavir given alone every eight hours. Combinations of indinavir and ritonavir that contained 800 mg of indinavir and either 200 or 400 mg of ritonavir resulted in higher plasma indinavir concentrations than a combination with 400 mg of indinavir and 400 mg or ritonavir. A combination of indinavir 800 mg and ritonavir 100 mg resulted in higher total exposure and peak levels than those seen with indinavir 400 mg / ritonavir 400 mg, however, the trough levels for these regimens were similar. Plasma ritonavir concentrations after treatment arms containing 100 or 200 mg of ritonavir were increased by its use with indinavir but no effect on ritonavir levels was noted for regimens containing 400 mg of ritonavir. Finally, the combination of indinavir and ritonavir appeared to remove any food effect on indinavir pharmacokinetics but not ritonavir pharmacokinetics. Reports in the scientific literature have raised concerns about the safety and tolerability of indinavir and ritonavir combination therapy. There was a high incidence of treatment related adverse events in

this study, but there were too few subjects in the treatment arms to discern any toxicity difference between different combinations of indinavir and ritonavir. In conclusion, the results of Merck 078 showed that plasma indinavir concentrations were increased when indinavir was given in combination with ritonavir. However, the identification of the optimal indinavir and ritonavir combination cannot be determined by the results of this study and must be identified in a large safety and efficacy trial of HIV-infected adults.

III. Labeling Proposal

The sponsor has proposed adding the following paragraphs to the Clinical Pharmacology, *Drug Interactions* section of the Crixivan package insert:



IV. Conclusions

The use of indinavir and ritonavir in combination in Merck 078 resulted in plasma indinavir concentrations that were substantially higher than those previously seen with the approved indinavir dose of 800 mg every eight hours. In Merck 078, the indinavir AUC was increased 159% with indinavir 800 mg / ritonavir 100 mg, 246% with indinavir 800 mg / ritonavir 200 mg, and 202% with indinavir 800 mg / ritonavir 400 mg. Because of the large increases in indinavir exposure when indinavir and ritonavir were used in combination, safety information from studies of adults receiving indinavir 800 mg every eight hours cannot be extrapolated to adults receiving an indinavir / ritonavir combination. In addition, safety concerns regarding the high indinavir concentrations seen with the use of indinavir with ritonavir are further substantiated by the narrow therapeutic window for indinavir seen in preclinical animal studies, the increased incidence of adverse events noted when 1000 mg of indinavir was given every eight hours, and evidence of increased toxicity of indinavir and ritonavir combinations reported in the scientific literature.[2-8] Therefore, we recommend that the sponsor pool the safety

data from their studies and from other clinical trials of indinavir and ritonavir coadministered in HIV-infected adults and submit this data to the Division for a more comprehensive review.

V. Recommendations for Regulatory Action

This supplement cannot be approved because of the small amount of safety data for HIV-infected adults with indinavir plasma concentrations that are much higher than those seen with the approved dose of indinavir. The sponsor will be asked to provide additional information regarding the safety of the coadministration of indinavir and ritonavir in HIV-infected adults via telephone facsimile.

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/BiopharmTL/KReynolds
HFD-530/Biopharm/RKumi
HFD-530/MOTL/SKukich
HFD-530/MO/MBaylor
HFD-530/CSO/CLincoln

VI. References

1. Crixivan package insert.

2. Becker S and Hoetelmans RMW. Exploiting pharmacokinetics to optimize antiretroviral therapy. www.hiv.medscape.com/Medscape/HIV/ClinicalMgmt/CM.v17/public/index-CM.v17.html. March 29, 2001.

3. Gatell JM, Lange J, Arnaiz JA, et al. A randomized study comparing continued indinavir (800 mg tid) vs switching to indinavir/ritonavir (800/100 mg bid) in HIV patients having achieved viral load suppression with indinavir plus 2 nucleoside analogues: the BID Efficacy and Safety Trial (BEST). XIII International AIDS Conference: July 9-14, 2000; Durban, South Africa. Abstract WeOrB484.

4. DeJesus E, Pistole M, Fetchick R, et al. A randomized, controlled, open-label study comparing the adherence and convenience of continuing indinavir Q8H vs switching to norvir/indinavir 400 mg/400 mg BID (the NICE Study). XIII International AIDS Conference: July 9-14, 2000; Durban, South Africa. Abstract WeOrB482.

5. Lamotte C, Peytavin G, Perre P, et al. Increasing adverse events with indinavir dosages and plasma concentrations in four different ritonavir-indinavir-containing regimens in HIV-infected patients. Eight Conference on Retroviruses and Opportunistic Infections: January 2001; Chicago, IL. Abstract 738.

6. Hsu A, Zolopa A, Shulman N, et al. Final analysis of ritonavir intensification in indinavir recipients with detectable HIV RNA levels. Eight Conference on Retroviruses and Opportunistic Infections: January 2001; Chicago, IL. Abstract 337.

7. Boyd M, Duncombe C, Newell M, et al. Indinavir/ritonavir vs indinavir in combination with AZT/3TC for treatment of HIV in nucleoside-experienced patients: a randomised, open-label trial. Eight Conference on Retroviruses and Opportunistic Infections: January 2001; Chicago, IL. Abstract 335.

8. Barreiro P, Soriano V, Oller V, and Gonzalez-Lahoz J. Potent activity but limited tolerance of ritonavir plus indinavir in salvage interventions. J Acquir Immune Defic Syndr Hum Retrovirol. 200; 24:488.

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

/s/

Mellisse Baylor
4/26/01 02:21:08 PM
MEDICAL OFFICER

Stanka Kukich
5/8/01 03:52:08 PM
MEDICAL OFFICER

Debra Birnkrant
5/14/01 04:10:27 PM
MEDICAL OFFICER

Christine Lincoln
5/15/01 10:46:33 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-046, S-047

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20685 SLR 046 and 047
Submission Dates: 03/30/2000, 12/14/2001, 01/22/2002, 07/10/2002, 07/15/2002, 04/23/2003, 05/08/2003, 06/20/2003 and 10/27/2003
Brand Name: Crixivan
Generic Name: indinavir sulfate
Formulation: 100, 200, 333 and 400 mg capsules
Applicant: Merck and Co., Inc
Reviewer: Robert O. Kumi, Ph.D.
Team Leader: Kellie Reynolds, Pharm.D.

I. Executive Summary

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the information submitted to NDA 20685 SLR 046 and 047 finds the information acceptable.

- SLR 046

The information provided in SLR 046 is adequate to change the Clinical Pharmacology, Contraindications and Precautions sections of the Crixivan label to make it comparable to that of other protease inhibitors. Extensive discussions were held between the applicant and the FDA to arrive at an acceptable Crixivan label; the applicant was issued an "Approvable letter" on April 30, 2003 because of unresolved issues. These deficiencies have been resolved and the Crixivan labeling is finalized. SLR 046 provides new drug-drug interaction information regarding coadministration of theophylline with indinavir and coadministration of saquinavir (hard and soft gel) with indinavir.

- SLR 047

The information provided in SLR 047 is adequate to update the existing Crixivan label, regarding drug-drug interactions between indinavir and ritonavir. However, no dosing recommendations can be made regarding the combination of indinavir and ritonavir because the safety and efficacy of these regimens have not been sufficiently evaluated and no exposure-response relationship exists for the studied regimens.

[ ]

B. Phase IV Commitments:

Not applicable.

C. Summary of Clinical Pharmacology Findings

NDA 20685 SLR 046 and 047 included drug-drug interaction study reports and reorganization of drug-drug interaction information in the Crixivan™ (indinavir sulfate) label. SLR 046 includes revised labeling information and study reports for indinavir-theophylline (Study 049) and indinavir-saquinavir (Study 051). SLR 047 includes the indinavir-ritonavir drug interaction study report (Study 078). These two supplements were reviewed simultaneously because they were submitted at about the same time and the information for SLR 046 was included in SLR 047. Crixivan (indinavir sulfate) and Norvir™ (ritonavir) are HIV protease inhibitors approved for the treatment of HIV in combination with other antiretroviral agents.

Regulatory Background

NDA 20685 SLR 046 and 047 were originally submitted to the FDA in March 2000. The applicant and FDA have had numerous discussions regarding these supplements, which culminated in an Approvable Action on April 30 2003. An approvable action was granted because (1) the applicant had not provided adequate scientific rationale for proposing to label simvastatin and lovastatin in a similar manner to

atorvastatin (2) the applicant had not provided clinical study reports for the indinavir-theophylline (Study 049) or indinavir-saquinavir (Study 051) interaction.

The June 20, 2003 submissions included the above study reports; however, the submissions do not include information regarding the lovastatin/simvastatin vs. atorvastatin labeling issue. Previously, the applicant suggested that indinavir could be coadministered with simvastatin, lovastatin or atorvastatin in a similar manner, but the applicant did not provide a scientific basis for this labeling recommendation. The currently proposed Crixivan package insert labels atorvastatin differently from the other two statins, which is consistent with labeling of statins with other protease inhibitors.

Relevant results from the Crixivan (indinavir sulfate) + Norvir (ritonavir) study (Study 078, SLR 047), Crixivan + Saquinavir (Study 051, SLR 046), and Crixivan + Theophylline (Study 049, SLR 046) drug-drug interaction studies are summarized in Tables I and II.

Table I: Pharmacokinetic Parameters for Indinavir in the Presence of the Coadministered Drug

Coadministered drug	**Dose of Coadministered drug (mg)**	**Dose of CRIXIVAN (mg)**	**n**	**Ratio (with/without coadministered drug) of Indinavir Pharmacokinetic Parameters (90% CI)**		
				C_{max}	AUC	C_{min}
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 16[4]	1.59 (1.34, 1.89)	2.69 (2.16, 3.35)[5]	10.94 (7.22, 16.56)[6]
Ritonavir	200 twice daily, 14 days	800 twice daily, 14 days	9, 16[4]	1.76 (1.47, 2.11)	3.55 (2.83, 4.45)[5]	24.43 (15.91, 37.51)[6]

[4] Comparison to historical data on 16 subjects receiving indinavir alone.
[5] To estimate $AUC_{0\text{-}24hr}$: $AUC_{0\text{-}12hr}$ multiplied by 2 for indinavir + Ritonavir; $AUC_{0\text{-}8hr}$ multiplied by 3 for indinavir alone.
[6] C_{12hr} for indinavir + ritonavir; C_{8hr} for indinavir alone.

Table II: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Indinavir

Coadministered drug	**Dose of Coadministered drug (mg)**	**Dose of CRIXIVAN (mg)**	**n**	**Ratio (with/without CRIXIVAN) of Coadministered Drug Pharmacokinetic Parameters (90% CI)**		
				C_{max}	AUC	C_{min}
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 4[3]	1.61 (1.13, 2.29)	1.72 (1.20,2.48)	1.62 (0.93, 2.85)
	200 twice daily, 14 days	800 twice daily, 14 days	9,5[3]	1.19 (0.85, 1.66)	1.96 (1.39, 2.76)	4.71 (2.66, 8.33) n=9, 4
Saquinavir						
Hard gel formulation	600 single dose	800 three times daily, 2 days	6	4.7 (2.7, 8.1)	6.0 (4.0, 9.1)	2.9 (1.7, 4.7)[4]
Soft gel formulation	800 single dose	800 three times daily, 2 days	6	6.5 (4.7, 9.1)	7.2 (4.3, 11.9)	5.5 (2.2, 14.1)[4]
Soft gel formulation	1200 single dose	800 three times daily, 2 days	6	4.0 (2.7, 5.9)	4.6 (3.2, 6.7)	5.5 (3.7, 8.3)[4]
Theophylline	250 single dose (on Days 1 and 7)	800 three times daily, 6 days (Days 2 to 7)	12,4[3]	0.88 (0.76, 1.03)	1.14 (1.04, 1.24)	1.13 (0.86, 1.49) n=7, 3

[3] Parallel group design; n for co-administered drug + indinavir, n for coadministered drug alone.
[4] C_{6hr}

All the listed drug-drug interaction studies were conducted in healthy volunteers. In brief, the data indicate the following:

- Coadministration of indinavir with ritonavir increases indinavir exposure (AUC ~ 3-fold, C_{max} ~ 1.5-fold and C_{min} > 10-fold); the magnitude of the increase appears to be dependent on the ritonavir dose.
- Coadministration of indinavir with saquinavir increases saquinavir AUC and C_{max} by at least 2-fold
- Coadministration of indinavir with theophylline does not affect theophylline exposure.

Dosing recommendations for coadministration of indinavir with ritonavir, saquinavir or theophylline In the absence of adequate exposure-response, efficacy and safety data it is not possible to make a dosing recommendation regarding indinavir coadministration with either saquinavir or ritonavir. However, the absence of these data does not preclude incorporating the study results in the Crixivan label. The theophylline-indinavir study findings indicate that theophylline can be coadministered with indinavir without theophylline dose modification. Please refer to the individual study reviews for additional information.

Labeling Changes The major change to the Crixivan label is related to the presentation of the drug-drug interaction information; the Kaletra (lopinavir/ritonavir) label was used as a labeling guideline. This change makes the Crixivan label informationally and stylistically comparable to that of other protease inhibitors. Key drug-drug interaction labeling changes are enumerated as follows:

Clinical Pharmacology Section

1. Inclusion of information about the role of CYP enzymes (overview)
- statement included to indicate indinavir inhibits CYP3A4 and may be a weak inhibitor of CYP2D6
- statement included to indicate indinavir is metabolized by CYP3A4
- statement included to indicate indinavir does not inhibit other CYP enzymes
2. Conversion of drug-drug interaction information from text format to a tabular format
3. Inclusion of drug-drug interaction information for coadministration of indinavir with ritonavir, theophylline, and saquinavir
4. Inclusion of drug-drug interaction information for coadministration of indinavir with vardenafil and tadalafil; the Office of Clinical Pharmacology and Biopharmaceutics (DRUDP affiliated) reviewed the vardenafil and tadalafil studies.
5. Update the drug-drug interaction information for coadministration of indinavir with efavirenz, based on new information in the SUSTIVA label.

Contraindications Section

Information in existing text is reiterated in table. Contraindicated drug classes are antiarrhythmics, ergot derivatives, sedative/hypnotics, GI motility agents, and neuroleptics.

Precautions: Drug Interactions

1. Inclusion of information about the role of CYP enzymes as in Clinical Pharmacology Section
2. Conversion of drug-drug interaction information from text format to a tabular format (two tables). The first table describes "Drugs that should not be coadministered with Crixivan" and the other table describes "Established and other potentially significant drug interactions".
3. Update drug-drug interaction tables, to be consistent with new information in the Clinical Pharmacology Section.

Dosage and Administration

known.

_____ Date_____
Robert O. Kumi, Ph. D.
Clinical Pharmacology Reviewer

Concurrence

_____ Date_____
Kellie Reynolds, Pharm. D.
Clinical Pharmacology Team Leader

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

/s/

Robert Kumi
5/12/04 11:03:19 AM
BIOPHARMACEUTICS

Kellie Reynolds
5/12/04 02:58:47 PM
BIOPHARMACEUTICS