

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-685 / S-060

Trade Name: Crixivan

Generic Name: (indinavir sulfate)

Sponsor: Merck & Co.

Approval Date: December 23, 2004

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APPLICATION NUMBER:

20-685 / S-060

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-060

APPROVAL LETTER



NDA 20-685/S-060

PRIOR APPROVAL SUPPLEMENT

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 application dated May 14, 2004, received May 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crixivan® (indinavir sulfate) capsules.

This supplemental new drug application provides for the following changes to the package insert:

1. The **CLINICAL PHARMACOLOGY: Pharmacokinetics: *Pregnant Patients*** section was updated to include information from a study (PACTG 358) of 16 HIV infected pregnant patients at 14 to 28 weeks gestation at enrollment. An optimal dosing regimen has not been established.
2. The **PRECAUTIONS: Pregnancy: *Pregnancy Category C*** section was also revised to include information from Study PACTG 358.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon 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-060."
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).

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

/s/

Debra Birnkrant
12/23/04 11:40:22 AM
NDA 20-685

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-060

LABELING

CRIXIVAN®

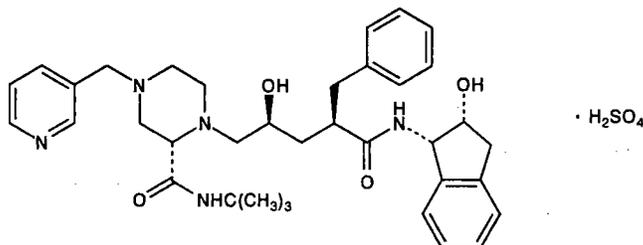
(INDINAVIR SULFATE)

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

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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 \pm 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 $30,691 \pm 11,407$ nM \cdot hour ($n=16$), peak plasma concentration (C_{max}) was $12,617 \pm 4037$ 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 $77\% \pm 8\%$ reduction in AUC and an $84\% \pm 7\%$ 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, $83 \pm 1\%$ ($n=4$) and $19 \pm 3\%$ ($n=6$) 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 $10.4 \pm 4.9\%$ ($n=10$) and $12.0 \pm 4.9\%$ ($n=10$) 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:

| PK Parameter | % change in PK parameter for females relative to males | 90% Confidence Interval |
|-----------------------------|--|-------------------------|
| AUC _{0-8h} (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_{0-8hr} 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.

Pregnant Patients: The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A CRIXIVAN dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). The mean indinavir plasma AUC_{0-8hr} at weeks 30-32 of gestation (n=11) was 9231 nM•hr, which is 74% (95% CI: 50%, 86%) lower than that observed 6 weeks postpartum. Six of these 11 (55%) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in non-pregnant patients in another study (see PRECAUTIONS, *Pregnancy*).

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 (<i>Hypericum perforatum</i> , 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 days | 800 three times daily, 7 days | 11 | 0.95 (0.80, 1.11) | 0.95 (0.80, 1.12) | 1.13 (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 CRIVIVAN (mg) | n | Ratio (with/without CRIVIVAN) 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 300 once daily in the morning, 10 days | 800 three times daily, 10 days | 14 10 | 1.29 (1.05, 1.59) | 1.54 (1.33, 1.79) | 1.99 (1.71, 2.31) n=13 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 | 18 | See text below for discussion of interaction. | | |

| daily | | | | | | |
|------------------------------------|--------------------------------------|-----------------------------------|-------------------|----------------------|----------------------|--------------------------------|
| 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_{0-8hr} 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.

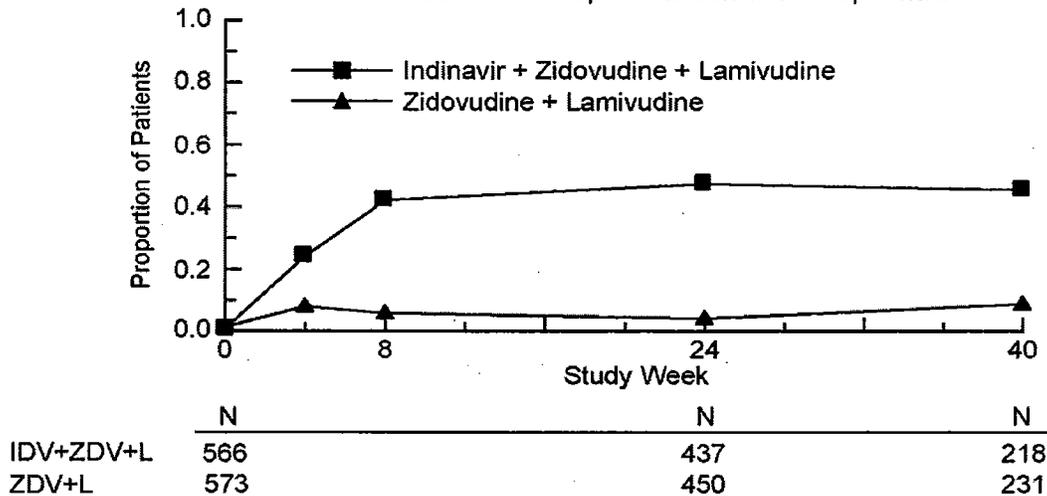
Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of CRIXIVAN in combination with zidovudine and lamivudine with that of zidovudine plus lamivudine on the progression to an AIDS-defining illness (ADI) or death. Patients were protease inhibitor and lamivudine naive and zidovudine experienced, with CD4 cell counts of ≤ 200 cells/mm³. 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/mm³. The mean baseline HIV RNA was 4.95 log₁₀ 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.

| 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

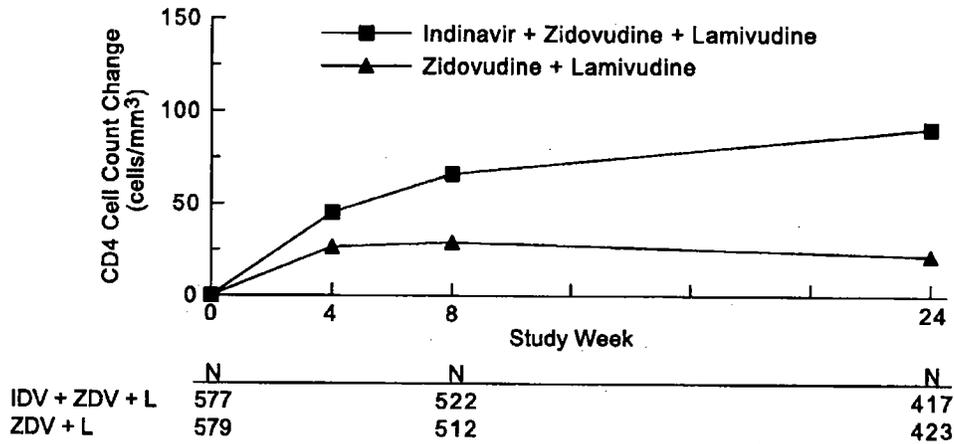
Study ACTG 320: Figure 1

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



Study ACTG 320: Figure 2

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



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/mm³. 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/mm³, mean serum viral RNA of 4.44 log₁₀ 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.

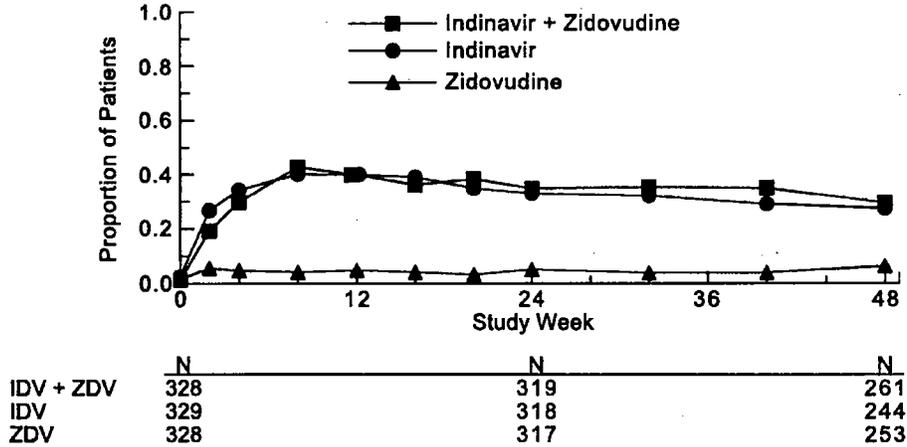
Table 5
Protocol 028

| 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.

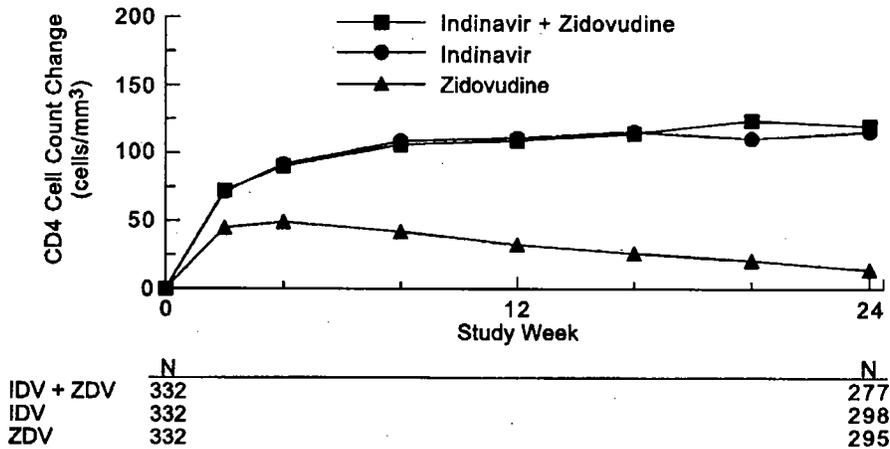
Study 028: Figure 3

Indinavir Protocol 028 Zidovudine Naive
Viral RNA - Proportions Below 500 Copies/mL in Serum



Study 028: Figure 4

Indinavir Protocol 028 Zidovudine Naive
CD4 Cell Counts - Mean Change from Baseline

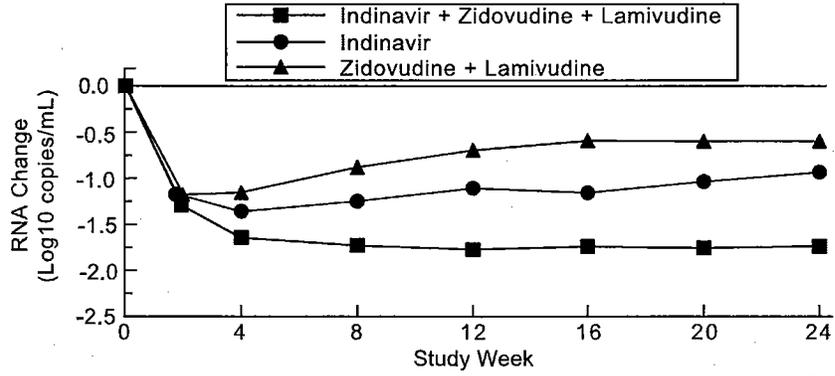


Study 035 was a multicenter, randomized trial in 97 HIV-1 seropositive patients who were zidovudine-experienced (median exposure 30 months), protease-inhibitor- and lamivudine-naive, with mean baseline CD4 count 175 cells/mm³ and mean baseline serum viral RNA 4.62 log₁₀ copies/mL (41,230 copies/mL). 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 log₁₀ 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

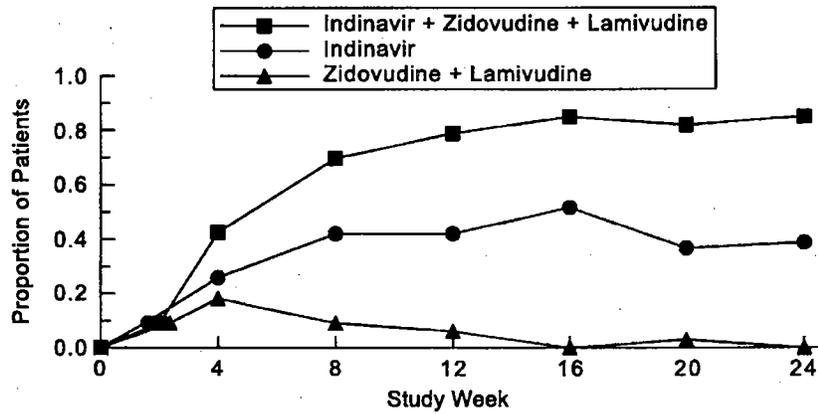
Indinavir Protocol 035 Zidovudine Experienced
Viral RNA - Mean Log₁₀ Change from Baseline in Serum



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

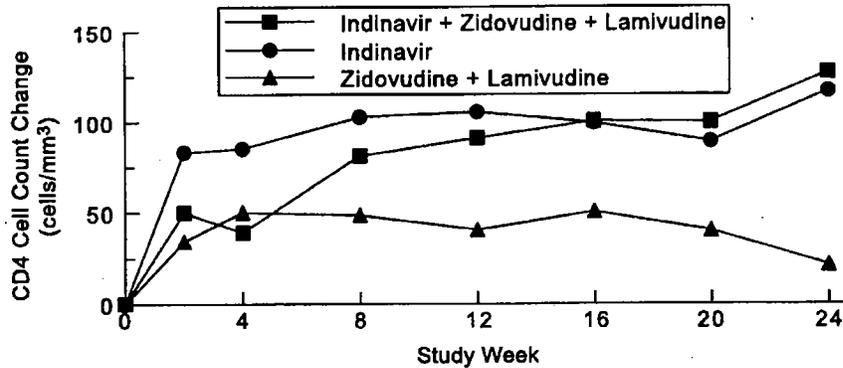
Study 035: Figure 6

Indinavir Protocol 035 Zidovudine Experienced
Viral RNA - Proportions Below 500 Copies/mL in Serum



Study 035: Figure 7

Indinavir Protocol 035 Zidovudine Experienced
CD4 Cell Counts - Mean Change from Baseline



| | 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 (<i>Hypericum perforatum</i>) | 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 Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine | ↑ dihydropyridine calcium channel blockers concentration | Caution is warranted and clinical monitoring of patients is recommended. |
| 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 patients. CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A CRIXIVAN dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). Given the substantially lower antepartum exposures observed and the limited data in this patient population, indinavir use is not recommended in HIV-infected pregnant patients (see CLINICAL PHARMACOLOGY, *Pregnant Patients*).

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients 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/m² 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 not 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 \geq 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 \leq 2.4 g/day.

Clinical adverse experiences reported in \geq 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

| Adverse Experience | 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 | |
|--|--|---|----------------------------------|--|---|
| | 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) |
| <i>Body as a Whole</i> | | | | | |
| 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 |
| <i>Digestive System</i> | | | | | |
| 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 |
| <i>Hemic and Lymphatic System</i> | | | | | |
| Anemia | 0.6 | 1.2 | 2.1 | 2.4 | 3.5 |
| <i>Musculoskeletal System</i> | | | | | |
| Back pain | 8.4 | 4.5 | 1.5 | 0.9 | 0.7 |
| <i>Nervous System/Psychiatric</i> | | | | | |
| 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 |
| <i>Skin and Skin Appendage</i> | | | | | |
| Pruritus | 4.2 | 2.4 | 1.8 | 0.5 | 0 |
| Rash | 1.2 | 0.6 | 2.4 | 1.1 | 0.5 |
| <i>Respiratory System</i> | | | | | |
| 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 |
| <i>Urogenital System</i> | | | | | |
| Nephrolithiasis/uroolithiasis* | 8.7 | 7.8 | 2.1 | 2.6 | 0.3 |
| Dysuria | 1.5 | 2.4 | 0.3 | 0.4 | 0.2 |
| <i>Special Senses</i> | | | | | |
| 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

| | CRIXIVAN Percent (n=329) | Study 028 | Zidovudine | Study ACTG 320 | |
|---|--------------------------------|--|--------------------|--|--|
| | | CRIXIVAN plus Zidovudine Percent (n=320) | Percent (n=330) | CRIXIVAN plus Zidovudine plus Lamivudine Percent (n=571) | Zidovudine plus Lamivudine Percent (n=575) |
| <i>Hematology</i> | | | | | |
| Decreased hemoglobin <7.0 g/dL | 0.6 | 0.9 | 3.3 | 2.4 | 3.5 |
| Decreased platelet count <50 THS/mm ³ | 0.9 | 0.9 | 1.8 | 0.2 | 0.9 |
| Decreased neutrophils <0.75 THS/mm ³ | 2.4 | 2.2 | 6.7 | 5.1 | 14.6 |
| <i>Blood chemistry</i> | | | | | |
| 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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-685 / S-060

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



Memorandum of Project Manager's Review: Prior Approval Supplement

NDAs: 20-685/S-060 Crixivan® (indinavir sulfate) capsules

Date submitted: May 14, 2004

Date received: May 17, 2004

Date completed: December 14, 2004

Sponsor: Merck & Co., Inc.
P.O. Box 2000, RY 33-720
Rahway, NJ 07065

Product: Crixivan® (indinavir sulfate) capsules

Materials Reviewed:

Labeling Supplement-Prior Approval (package insert) was compared to the last approved package insert (NDA 20-685/S-046 and 047, approved May 7, 2004). Approved supplements 046 and 047 also included revisions approved on January 12, 2004 in S-058.

Background:

This Labeling Supplement-Prior Approval provides for the following changes to the package insert:

1. The **CLINICAL PHARMACOLOGY: Pharmacokinetics: *Pregnant Patients*** section was updated to include information from a study (PACTG 358) of 16 HIV infected pregnant patients at 14 to 28 weeks gestation at enrollment. An optimal dosing regimen has not been established.
2. The **PRECAUTIONS: Pregnancy: *Pregnancy Category C*** section was also revised to include information from Study PACTG 358.

Review Summary:

The revisions are described below. There were no changes to the patient package insert.

Revisions to the Package Insert

1. The following was added to the **CLINICAL PHARMACOLOGY: Pharmacokinetics: *Pregnant Patients*** section:

“Pregnant Patients: The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A CRIVAN dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). The mean indinavir plasma AUC_{0-8hr} at weeks 30-32 of gestation (n=11) was 9231 nM•hr, which is 74% (95% CI: 50%, 86%) lower than that observed 6 weeks postpartum. Six of these 11 (55%) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in non-pregnant patients in another study (see PRECAUTIONS, *Pregnancy*).”

2. The following was added to the **PRECAUTIONS: Pregnancy: *Pregnancy Category C*** section:

“A CRIVAN dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). Given the substantially lower antepartum exposures observed and the limited data in this patient population, indinavir use is not recommended in HIV-infected pregnant patients (see CLINICAL PHARMACOLOGY, *Pregnant Patients*).”

Conclusions/Recommendations:

This labeling supplement, submitted on May 14, 2004 is acceptable. Please note that this supplement fulfills the applicant's only remaining OPEN postmarketing commitment. Please see the Medical Officer's review and Medical Team Leader's concurrence. An approval letter should be sent to the applicant as well as a fulfillment of postmarketing commitment letter.

Virginia L. Behr
Chief, Project Management Staff
Division of Antiviral Drug Products
FDA

**This is a representation of an electronic record that was signed electronically and
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/s/

Virginia Behr
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