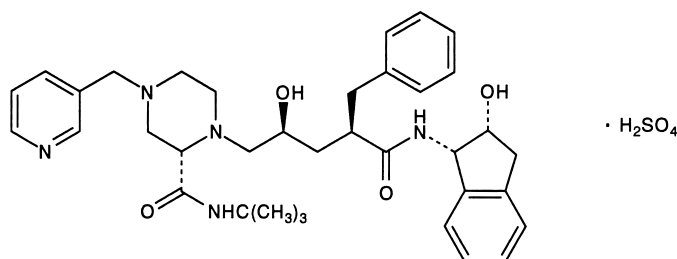


CRIXIVAN® **(INDINAVIR SULFATE)** **CAPSULES**

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, and 400 mg of indinavir (corresponding to 125, 250, 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 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 IC₉₅ values of 50-100 nM. At or following viral RNA rebound (after 12-76 weeks of therapy), IC₉₅ 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•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 ¹⁴C-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:

Table 1

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)
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)
		After evening dose		0.71 ¹ (0.57, 0.89)	0.54 ¹ (0.46, 0.63)	0.43 ¹ (0.37, 0.50)
		400 single dose	10	0.65 (0.53, 0.79)	0.73 (0.60, 0.87)	0.90 (0.71, 1.15)
Grapefruit Juice	8 oz.	400 single dose	10	0.95 (0.88, 1.03)	0.99 (0.87, 1.13)	0.89 (0.75, 1.06)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 7 days	11	0.78 ¹ (0.69, 0.88)	0.99 ¹ (0.91, 1.06)	1.49 ¹ (1.28, 1.74)
Itraconazole	200 twice daily, 7 days	600 three times daily, 7 days	12	0.69 ¹ (0.61, 0.78)	0.80 ¹ (0.74, 0.87)	1.29 ¹ (1.11, 1.51)
Ketoconazole	400 once daily, 7 days	600 three times daily, 7 days	12	0.42 ¹ (0.37, 0.47)	0.44 ¹ (0.41, 0.48)	0.73 ¹ (0.62, 0.85)
	400 once daily, 7 days	400 three times daily, 7 days	12			
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 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) ¹	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	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 ⁵	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	10 single dose	800 three times daily	18	See text below for discussion of interaction.		
Zidovudine ⁵	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 ⁵						
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/Lamivudine⁵

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)
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All interaction studies conducted in healthy, HIV-negative adult subjects, unless otherwise indicated.

¹ Registered trademark of Ortho Pharmaceutical Corporation

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}

⁵ Study conducted in HIV-positive subjects.

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 a 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.

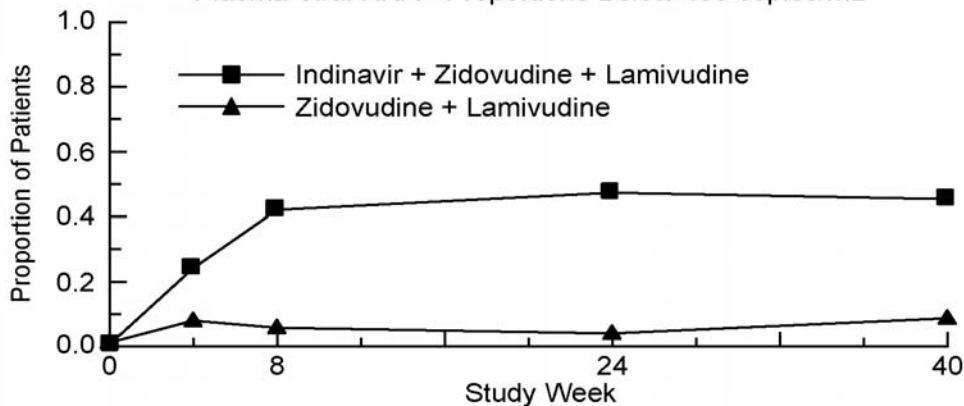
Table 4
ACTG 320

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

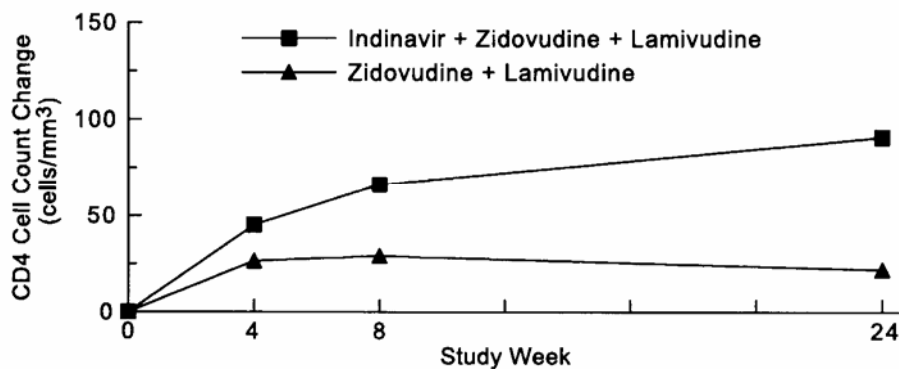
Indinavir Protocol ACTG 320 Zidovudine Experienced Plasma Viral RNA - Proportions Below 400 copies/mL



	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/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.

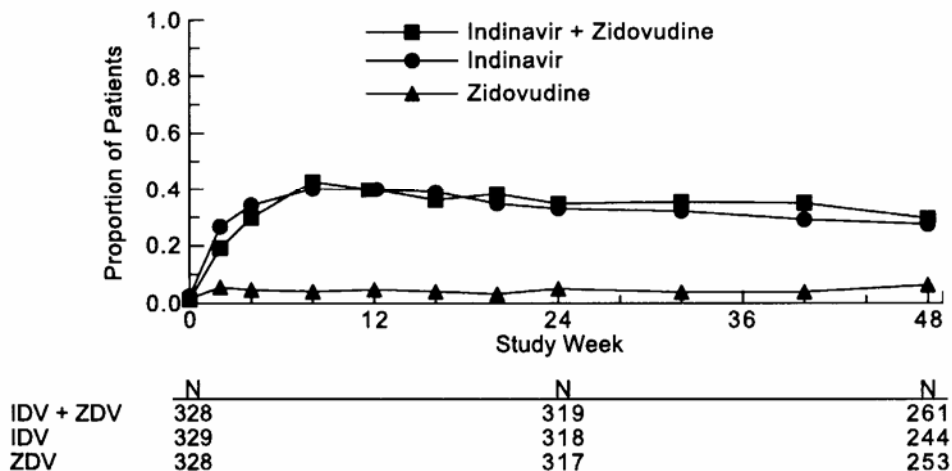
Table 5
Protocol 028

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.

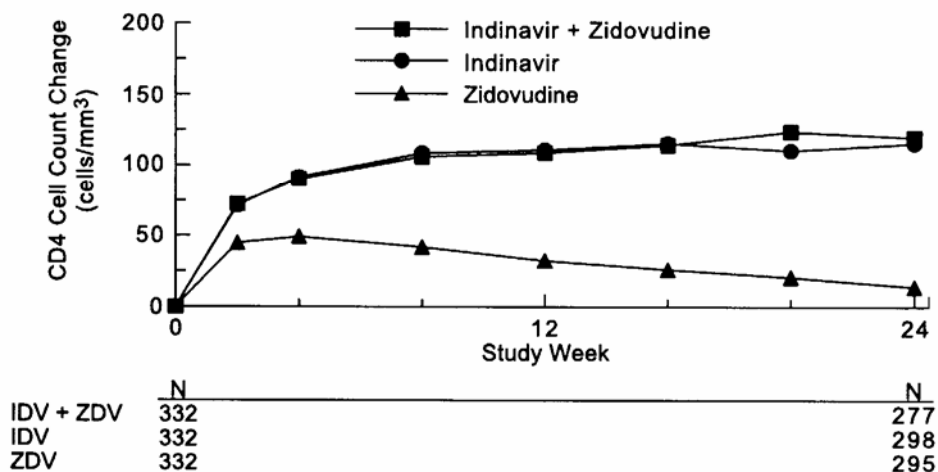
Study 028: Figure 3

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



Study 028: Figure 4

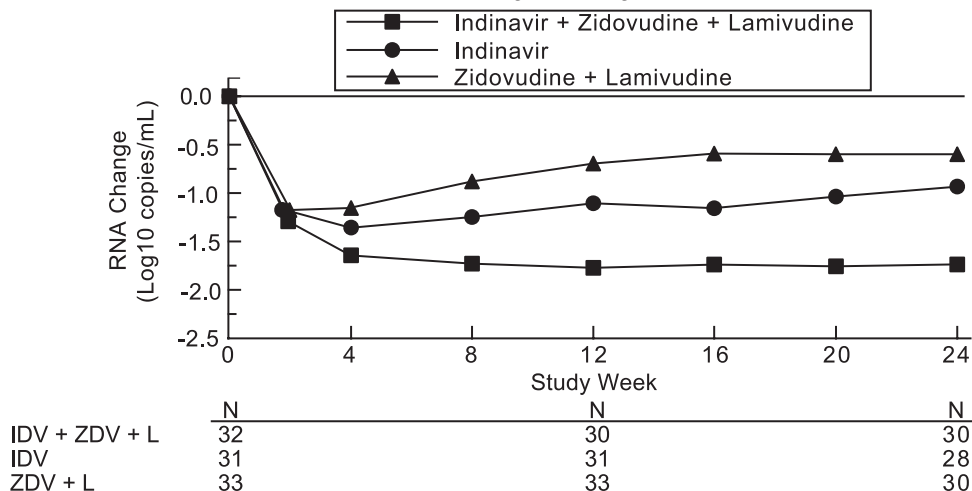
Indinavir Protocol 028 Zidovudine Naive
CD4 Cell Counts - Mean Change from Baseline



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.

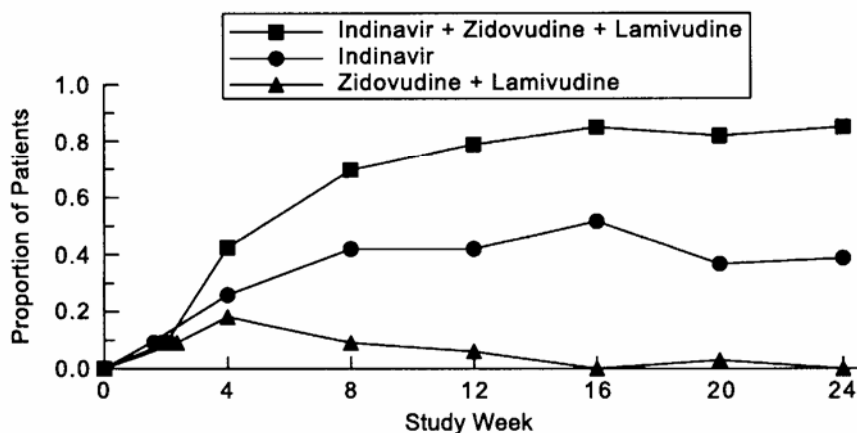
Study 035: Figure 5

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



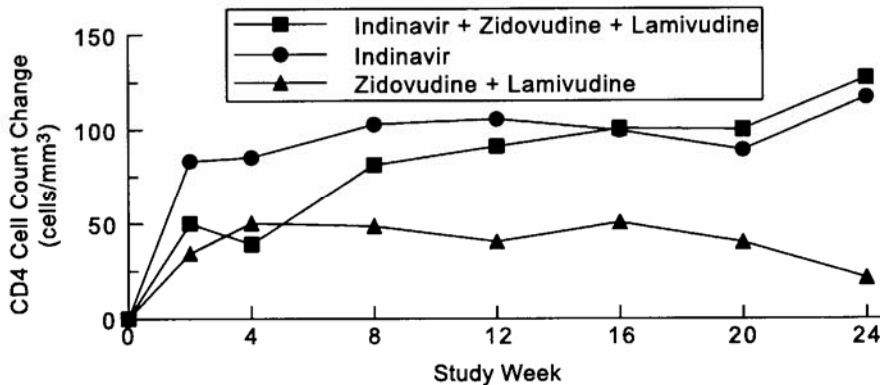
Study 035: Figure 6

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	Oral midazolam, triazolam, alprazolam
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, simvastatin, or rosuvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with atorvastatin. The interaction of CRIXIVAN with pravastatin and fluvastatin is not known. The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including CRIXIVAN, are used in combination with these statin drugs (see PRECAUTIONS, *Drug Interactions*).

Midazolam is extensively metabolized by CYP3A4. Co-administration with CRIXIVAN with or without ritonavir may cause a large increase in the concentration of this benzodiazepine. No drug interaction study has been performed for the co-administration of CRIXIVAN with benzodiazepines. Based on data from other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore CRIXIVAN should not be co-administered with orally administered midazolam (see CONTRAINDICATIONS), whereas caution should be used with co-administration of CRIXIVAN and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. If CRIXIVAN with or without ritonavir is co-administered with parenteral midazolam, it should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

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: Oral midazolam, triazolam, alprazolam	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, rosuvastatin	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: bepiridil, 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.
Inhaled/nasal steroid: Fluticasone	↑ fluticasone concentration	Concomitant use of fluticasone propionate and CRIXIVAN may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Fluticasone use is not recommended in situations where CRIXIVAN is coadministered with a potent CYP3A4 inhibitor such as ritonavir unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
HMG-CoA Reductase Inhibitors: atorvastatin, pravastatin, fluvastatin	↑ atorvastatin concentration pravastatin, fluvastatin- interaction not studied	Use the lowest possible dose of atorvastatin with careful monitoring. If no alternative treatment is available, use with careful monitoring.
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.
Midazolam (parenteral administration)	↑ midazolam concentration	Concomitant use of parenteral midazolam with CRIXIVAN may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with CRIXIVAN is CONTRAINDICATED (see Table 8).
Ketoconazole	↑ indinavir concentration	Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.
Rifabutin	↓ indinavir concentration	Dose reduction of rifabutin to half the standard dose and a dose

	↑ rifabutin concentration	increase of CRIXIVAN to 1000 mg 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.
Antidepressant: Trazodone	↑ trazodone concentration	Concomitant use of trazodone and CRIXIVAN may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as CRIXIVAN, the combination should be used with caution and a lower dose of trazodone should be considered.
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.
Venlafaxine	↓ indinavir concentration	In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C _{max} . Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.
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 $\geq 2\%$ 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	Study 028 CRIXIVAN plus Zidovudine	Zidovudine	Study ACTG 320 CRIXIVAN plus Zidovudine plus Lamivudine	Zidovudine plus Lamivudine
	Percent (n=329)	Percent (n=320)	Percent (n=330)	Percent (n=571)	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; renal insufficiency; renal failure; 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 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. 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® (indinavir sulfate)

9640610

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.

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