Merck Sharp & Dohme Corp., a subsidiary of
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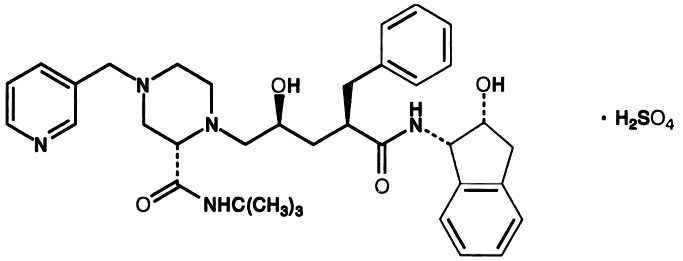
CRIXIVAN®
(INDINAVIR SULFATE)
CAPSULES

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 200 and 400 mg of indinavir (corresponding to 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 and titanium dioxide.

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 IC_{95} values of 50-100 nM. At or following viral RNA rebound (after 12-76 weeks of therapy), IC_{95} values ranged from 25 to >3000 nM, and the viruses carried 2 to 10 mutations in the protease gene relative to baseline.

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

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

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

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

Special Populations

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

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

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

Table 1

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

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

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

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

Pediatric: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m^2 every 8 hours, produced $AUC_{0\text{-}8hr}$ of 38,742 ± 24,098 nM•hour (n=34), C_{max} of 17,181 ± 9809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

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 $AUC_{0\text{-}8hr}$ 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* (0.48, 0.86)	No significant change*	2.18* (1.16, 4.12)
Delavirdine	400 three times daily	600 three times daily, 7 days	28	No significant change	1.53* (1.07, 2.20)	3.98* (2.04, 7.78)
Efavirenz†	600 once daily, 10 days	1000 three times daily, 10 days	20			
		After morning dose		No significant change*	0.67* (0.61, 0.74)	0.61* (0.49, 0.76)
		After afternoon dose		No significant change*	0.63* (0.54, 0.74)	0.48* (0.43, 0.53)
		After evening dose		0.71* (0.57, 0.89)	0.54* (0.46, 0.63)	0.43* (0.37, 0.50)
Fluconazole†	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* (0.69, 0.88)	0.99* (0.91, 1.06)	1.49* (1.28, 1.74)
Ketoconazole	400 once daily, 7 days	600 three times daily, 7 days	12	0.69* (0.61, 0.78)	0.80* (0.74, 0.87)	1.29* (1.11, 1.51)
	400 once daily, 7 days	400 three times daily, 7 days	12	0.42* (0.37, 0.47)	0.44* (0.41, 0.48)	0.73* (0.62, 0.85)
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‡	See text below for discussion of interaction.		
Ritonavir	200 twice daily, 14 days	800 twice daily, 14 days	9, 16‡	See text below for discussion of interaction.		
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
St. John's wort (*Hypericum perforatum*, standardized to 0.3 % hypericin)	300 three times daily with meals, 14 days	800 three times daily	8	Not Available	0.46 (0.34, 0.58)§	0.19 (0.06, 0.33)§
Stavudine (d4T)†	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†	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)†	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 9¶	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.
* Relative to indinavir 800 mg three times daily alone.
† Study conducted in HIV-positive subjects.
‡ Comparison to historical data on 16 subjects receiving indinavir alone.
§ 95% CI.
¶ Parallel group design; n for indinavir + coadministered drug, n for indinavir alone.

Table 3: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Indinavir (See PRECAUTIONS, Table 9 for Recommended Alterations in Dose or Regimen)

Coadministered drug	Dose of Coadministered drug (mg)	Dose of CRIXIVAN (mg)	n	Ratio (with/without CRIXIVAN) of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Clarithromycin	500 twice daily, 7 days	800 three times daily, 7 days	12	1.19 (1.02, 1.39)	1.47 (1.30, 1.65)	1.97 (1.58, 2.46) n=11
Efavirenz	200 once daily, 14 days	800 three times daily, 14 days	20	No significant change	No significant change	--
Ethinyl Estradiol (ORTHO-NOVUM 1/35)*	35 mcg, 8 days	800 three times daily, 8 days	18	1.02 (0.96, 1.09)	1.22 (1.15, 1.30)	1.37 (1.24, 1.51)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 8 days	11	1.34 (1.12, 1.60)	1.12 (1.03, 1.22)	1.00 (0.92, 1.08)
Methadone†	20-60 once daily in the morning, 8 days	800 three times daily, 8 days	12	0.93 (0.84, 1.03)	0.96 (0.86, 1.06)	1.06 (0.94, 1.19)
Norethindrone (ORTHO-NOVUM 1/35)*	1 mcg, 8 days	800 three times daily, 8 days	18	1.05 (0.95, 1.16)	1.26 (1.20, 1.31)	1.44 (1.32, 1.57)
Rifabutin 150 mg once daily in the morning, 11 days + indinavir compared to 300 mg once daily in the morning, 11 days alone	150 once daily in the morning, 10 days	800 three times daily, 10 days	14	1.29 (1.05, 1.59)	1.54 (1.33, 1.79)	1.99 (1.71, 2.31) n=13
	300 once daily in the morning, 10 days	800 three times daily, 10 days	10	2.34 (1.64, 3.35)	2.73 (1.99, 3.77)	3.44 (2.65, 4.46) n=9
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 4‡	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‡	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)§
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)§
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)§
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
Stavudine¶	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‡	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¶	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¶						
Zidovudine	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 7‡	1.23 (0.74, 2.03)	1.39 (1.02, 1.89)	1.08 (0.77, 1.50) n=5, 5

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