

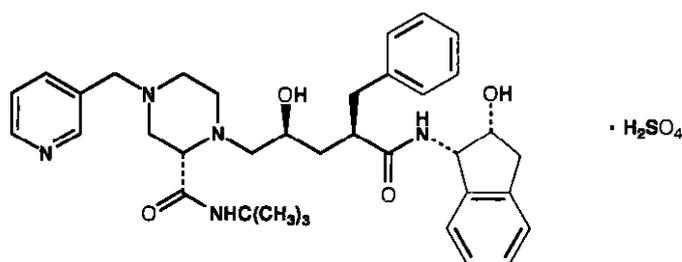
**PRODUCT INFORMATION****CRIXIVAN®****(Indinavir sulfate)****Capsules****NAME OF THE DRUG**

Indinavir sulfate

**DESCRIPTION**

CRIXIVAN (indinavir sulfate) is a specific protease inhibitor active against the Human Immunodeficiency Virus (HIV-1).

The chemical name for indinavir sulfate is (2*R*,4*S*)-2-benzyl-5-[(2*S*)-2- [(tert-butylamino) carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-*N*-[(1*S*,2*R*)-2,3-dihydro-2-hydroxy-1-indenyl] - 4-hydroxypentamide sulfate (1:1) (salt). Indinavir sulfate has the following structural formula:



Indinavir sulfate is a white to off-white, free-flowing crystalline powder with the molecular formula  $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$  and a molecular weight of 711.88. The CAS number is 157810-81-6.

CRIXIVAN capsules are formulated as a sulfate salt and are available for oral administration in strengths of 200 and 400mg of indinavir (corresponding to 250 and 500mg indinavir sulfate, respectively).

In addition to the active ingredient indinavir sulfate, each capsule contains the following inactive ingredients: anhydrous lactose, magnesium stearate, gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulfate.

**PHARMACOLOGY**

Indinavir inhibits purified HIV-1 and HIV-2 protease with an approximate tenfold selectivity for HIV-1 over HIV-2. The compound binds directly to the protease active site and, as such, is a competitive inhibitor of the enzyme. This inhibition prevents cleavage of the viral precursor polyprotein that occurs during maturation of the newly formed viral particle. The resulting immature particles are non-infectious and are incapable of establishing new cycles of infection. Indinavir did not significantly inhibit other eukaryotic proteases including human renin, human cathepsin D, human elastase, and human factor Xa.

®Registered Trademark of Merck & Co., Whitehouse Station, NJ, USA.

Studies of indinavir in animals to date have not used doses which resulted in systemic indinavir exposures significantly greater than those expected in humans treated at the recommended oral dose.

### Pharmacodynamics

#### Microbiology

Indinavir at concentrations of 50 to 100 nM mediated 95% inhibition ( $IC_{95}$ ) of viral spread (relative to an untreated virus-infected control) in human T-lymphoid cell cultures infected with several cell-line adapted variants of HIV-1 (LAI, MN, and RF). Similar inhibition of HIV-1 infection was seen in primary human monocytes/macrophages using a macrophage-tropic viral variant (SF 162). In addition, indinavir at concentrations of 25 to 100 nM resulted in 95% inhibition ( $IC_{95}$ ) of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including wild type virus and isolates resistant to reverse transcriptase inhibitors including zidovudine and non-nucleoside reverse transcriptase inhibitors. Synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the LAI variant of HIV-1 were incubated with indinavir and either zidovudine, didanosine, or a non-nucleoside reverse transcriptase inhibitor.

#### Drug Resistance

Loss of suppression of viral RNA levels occurred in some patients. When loss of viral RNA suppression occurred, it was typically associated with replacement of circulating susceptible virus with resistant variants. Resistance was correlated with the accumulation of mutations in the viral genome that resulted in the expression of amino acid substitutions in the viral protease enzyme.

At least eleven HIV-1 protease amino acid residue positions, at which substitutions are associated with resistance, have been identified: L10, K20, L24, M46, I54, L63, I64, A71, V82, I84, and L90. No single substitution was capable of engendering measurable (four-fold) resistance to the inhibitor; resistance was mediated by the co-expression of multiple and variable substitutions. In general, higher levels of resistance result from the co-expression of greater numbers of substitutions at the eleven identified positions. Substitutions at these positions appeared to accumulate sequentially, probably as the result of ongoing viral replication. Among patients experiencing viral RNA rebound during indinavir monotherapy at 800 mg q8h, substitutions at only three of these sites were observed in the majority of patients: V82 (to A or F), M46 (to I or L), and L10 (to I or R). Other substitutions were observed less frequently. The observed amino acid substitutions appeared to accumulate sequentially and in no consistent order, probably as a result of ongoing viral replication.

It should be noted that the decrease in suppression of viral RNA levels was seen more frequently when therapy with indinavir was initiated at doses lower than the recommended oral dose of 2.4 g/day. **Therefore, therapy with indinavir should be initiated at the recommended dose to increase suppression of viral replication and therefore inhibit the emergence of resistant virus.**

#### Cross-Resistance

HIV-1 patient isolates with reduced susceptibility to indinavir expressed varying patterns and degrees of cross-resistance to a series of diverse HIV protease inhibitors, including ritonavir and saquinavir. Complete cross-resistance was noted between indinavir and ritonavir; however, cross-resistance to saquinavir varied among isolates. Many of the protease amino acid substitutions reported to be associated with resistance to ritonavir and saquinavir were also associated with resistance to indinavir. The concomitant use of indinavir with a

nucleoside analogue (to which the patient is naive) may lessen the chance of the development of resistance to both indinavir and the nucleoside analogue. Cross-resistance between indinavir and HIV reverse transcriptase inhibitors is unlikely because the enzyme targets involved are different.

### Pharmacokinetic Properties

#### Absorption

Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration ( $T_{max}$ ) of 0.8 hours in adult subjects. Over the 200-1000 mg dose range administered in both healthy subjects and HIV-1 infected patients, there was a greater than dose-proportional increase in plasma concentrations of indinavir. At a dosing regimen of 800 mg every 8 hours, steady-state AUC (area under the plasma concentration time curve) was 27,813 nM hour (n=16),  $C_{max}$  (peak plasma concentration) was 11,144 nM (n=16), and  $C_{min}$  (trough plasma concentration) was 211 nM (n=16). At steady state, mean plasma concentrations of indinavir exceeded the  $IC_{95}$  for HIV-1 at all times during the dosing interval. As a result of the short half-life (1.8 hours, n=10), only a small increase in plasma concentrations occurred after multiple dosing (24% increase at 600mg every 6 hours and 12%, 20% and 24% respectively at 800mg every 8 hours, 1000mg every 8 hours and 800mg every 6 hours). Plasma pharmacokinetics were not changed after more than 70 weeks of continuous dosing at 600 mg every 6 hours.

In HIV-infected paediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m<sup>2</sup> every 8 hours, produced AUC<sub>0-8hr</sub> of 27,412 nM•hour (n=34),  $C_{max}$  of 12,182 nM (n=34), and trough concentration of 122 nM (n=29). The AUC and  $C_{max}$  values were generally similar to those previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours but the trough concentrations were lower in paediatric patients. Approximately 50% of the paediatric patients had trough values below 100nM, whereas approximately 10% of adult patients had trough levels below 100nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

#### Effect of Food on Oral Absorption

Administration of indinavir with a meal high in calories, fat, and protein resulted in a blunted and reduced absorption with an approximate 80% reduction in AUC and an 85% (n=10) reduction in  $C_{max}$ . Administration with light meals (e.g., dry toast with jam, apple juice, and coffee with skim milk and sugar or corn flakes, skim milk and sugar) resulted in a 2-8% reduction in AUC and  $C_{max}$  and in slightly increased variability of absorption between individuals. The plasma concentrations six and eight hours after administration of indinavir with these light meals were comparable to the corresponding fasted values. The concomitant use of grapefruit juice also resulted in a decreased absorption.

#### Distribution

Indinavir was not highly bound to human plasma proteins (39% unbound). Uptake into rat brain tissue was shown to be limited and the ratio of drug concentration in the brain to that in plasma averaged 0.18. Distribution of indinavir across the placental barrier was limited and the ratio of AUC in the foetus to that in maternal plasma averaged 0.02 to 0.2 in rabbits and rats respectively. Excretion of indinavir into the milk of lactating rats was extensive with the ratio of indinavir in milk to that in plasma averaging 1.26 to 1.45. Distribution into and out of the rat lymphatic system was shown to be rapid.

## Metabolism

Indinavir metabolism was evaluated in healthy subjects who received 400- and 1000-mg oral doses. Approximately 83% (n=4) and 19% (n=6) of the total radioactivity was recovered in the faeces and urine, respectively, following a 400-mg <sup>14</sup>C-radiolabeled dose. Seven major metabolites were identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies with human liver microsomes indicated that cytochrome CYP3A4 is the only P450 isozyme that plays a major role in the oxidative metabolism of indinavir. Analysis of plasma and urine samples from subjects who received indinavir indicated that indinavir metabolites contribute little to the overall *in vivo* protease inhibitory activity.

## Elimination

Over the 200-1000 mg dose range administered in both healthy subjects and HIV-1 infected patients, there was a slightly greater than dose-proportional increase in urinary recovery of indinavir. Renal clearance (116 mL/min, n=40) of indinavir is concentration-independent over the clinical dose range. Approximately 10% of indinavir is excreted unchanged renally. Mean urinary excretion of unchanged drug following single dose administration in the fasted state was 10.4% (n=10) following a 700-mg dose, and 12.0% (n=10) following a 1000-mg dose. Indinavir was rapidly eliminated with a half-life of 1.8 hours (n=10).

## Characteristics in Patients

### *Hepatic Insufficiency Due to Cirrhosis*

A study of twelve patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis gave evidence of decreased metabolism of indinavir resulting in approximately 60% higher mean AUC following a single 400-mg dose. The mean half-life of indinavir increased to approximately 2.8 hours. Patients with severe hepatic insufficiency have not been studied.

### *Renal Insufficiency*

The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency. Approximately 10% of indinavir is excreted unchanged renally.

### *Gender*

Pharmacokinetics of indinavir do not appear to be affected by gender.

### *Ethnicity*

Pharmacokinetics of indinavir do not appear to be affected by ethnic background.

### *Paediatric Patients*

In HIV-infected paediatric and adolescent patients (aged 3-18 years), a dose regimen of indinavir hard capsules, 500 mg/m<sup>2</sup> every 8 hours, produced AUC<sub>0-8h</sub> of 27,412 nM•hour (n=34), C<sub>max</sub> of 12,182 nM (n=34), and trough concentration of 122 nM (n=29). The AUC and C<sub>max</sub> values were generally similar to those previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours; the trough concentrations were lower in paediatric and adolescent patients. Approximately 50% of the paediatric patients had trough values below 100nM, whereas approximately 10% of adult patients had trough levels below 100nM. The relationship between specific trough values and inhibition of HIV replication has not been established. The pharmacokinetics of indinavir has not been studied in children aged less than 3 years. (see PHARMACOLOGY, *Absorption*).

### *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 patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). The geometric means of

indinavir plasma  $AUC_{0-8hr}$  and  $C_{max}$  of 11 patients at weeks 30-32 of gestation (ante-partum) were 9231 nM•hr and 5000 nM whilst the, observed values at 6 weeks postpartum were 34869 nM•hr and 13966 nM respectively. Indinavir  $AUC_{0-8hr}$  and  $C_{max}$  of ante-partum is significantly lower compared to 6 weeks postpartum (74% lower; 95% CI: 50%, 86%) Six of the 11 patient (55%) 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 PREGNANCY).

## CLINICAL TRIALS

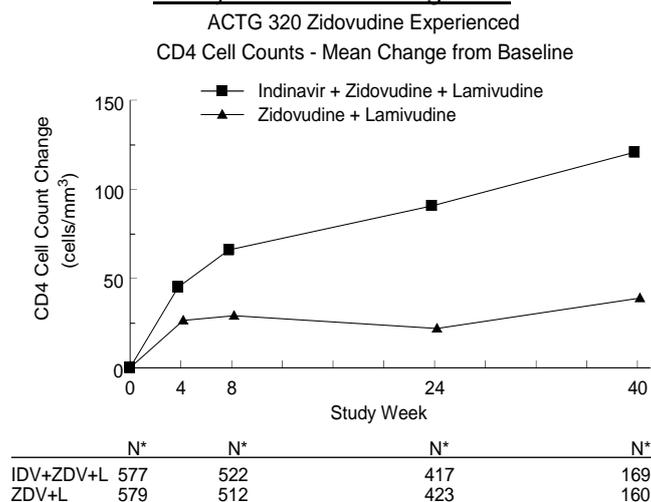
### Adults

Study ACTG 320 was a multicentre, randomised, double-blind clinical endpoint trial to compare the effect of CRIXIVAN in combination with zidovudine (or stavudine) and lamivudine with that of zidovudine (or stavudine) plus lamivudine on the progression to an AIDS-defining illness (ADI) or death. Patients were required to be protease inhibitor and lamivudine naive, and zidovudine experienced with CD4 cell counts of  $\leq 200$  cells/mm<sup>3</sup>. The study enrolled 1156 HIV-infected patients (17% female, 28% Black, 18% Hispanic, mean age 39 years, median time of prior zidovudine therapy 21 months). The median length of follow-up was 38 weeks with a maximum of 52 weeks.

There was a 50% reduction in the risk of progression to an ADI or death in the group treated with the combination containing CRIXIVAN relative to the group treated with the nucleoside analogue combination ( $p=0.001$ ). A total of 33 (6%) patients progressed to an ADI or death in the group treated with the combination containing CRIXIVAN compared to 63 (11%) patients in the group treated with the nucleoside analogue combination. In addition, there was a 49% reduction in the risk of overall mortality associated with CRIXIVAN. A total of 10 deaths (1.7%) occurred in the group treated with the combination containing CRIXIVAN and 19 deaths (3.3%) occurred in the group treated with the nucleoside analogue combination.

The mean baseline CD4 cell count over all patients was 87 cells/mm<sup>3</sup>. Mean changes in CD4 cell count are summarised in Figure 1.

Study ACTG 320: Figure 1



\*N = Number with CD4 cell count measurement at Weeks 0, 8, 24 and 40.

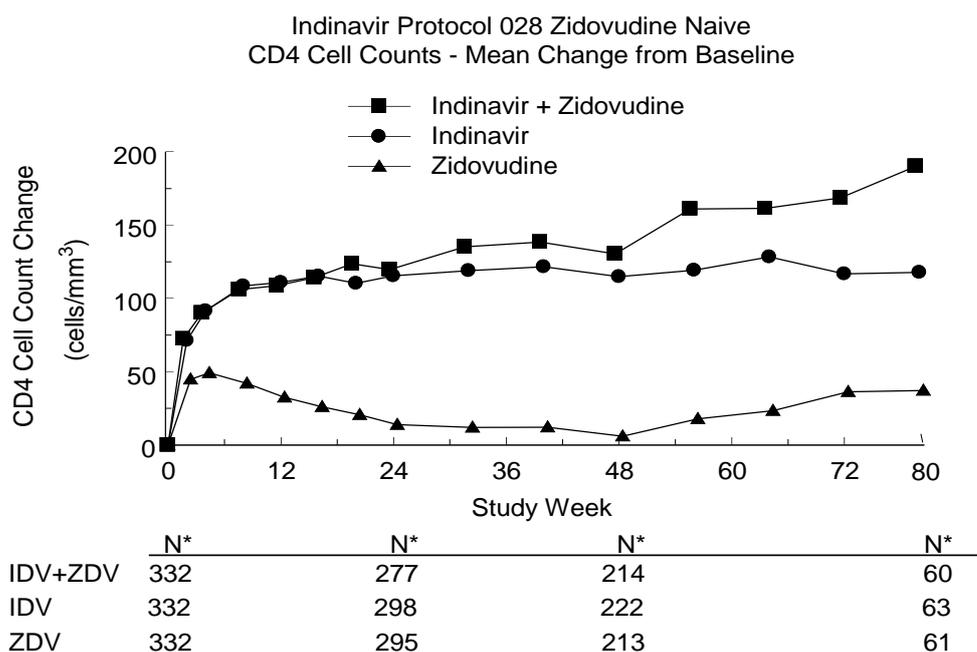
Study 028, a double-blind, multicentre, randomised, clinical endpoint trial compared the effects of CRIXIVAN plus zidovudine with those of CRIXIVAN alone or zidovudine alone on the progression to an ADI or death, and on surrogate marker responses. All patients were required to be antiretroviral naive with CD4 cell counts of 50 to 250 cells/mm<sup>3</sup>. The study enrolled 996 HIV-1 seropositive patients (28% female, 11% Black, 1% Asian/Other, median

age 33 years). Treatment regimens containing zidovudine were modified in a blinded manner with the optional addition of lamivudine (at median time study week 40). The median length of follow-up was 56 weeks with a maximum of 97 weeks.

There was a 70% reduction in the risk of progression to an ADI or death in the group initially treated with CRIXIVAN plus zidovudine compared to the group initially treated with zidovudine alone ( $p < 0.0001$ ). A total of 20 (6%) patients progressed to an ADI or death in the group treated with CRIXIVAN plus zidovudine compared to 61 (18%) patients in the group treated with zidovudine alone. There was a 61% reduction in the risk of progression to an ADI or death in the group treated with CRIXIVAN alone compared to the group treated with zidovudine alone ( $p < 0.0001$ ). A total of 26 (8%) patients progressed to an ADI or death in the group treated with CRIXIVAN alone. There was no statistically significant difference in the risk of progression to an ADI or death between the two groups receiving CRIXIVAN alone or in combination with zidovudine. A total of 8 (2.4%) deaths occurred in the group treated with CRIXIVAN plus zidovudine, 5 (1.5%) in the group treated with CRIXIVAN alone, and 11 (3.3%) in the group treated with zidovudine alone.

The mean baseline CD4 cell count over all patients was 152 cells/mm<sup>3</sup>, and the serum viral RNA was 4.44 log<sub>10</sub> copies/mL (27,824 copies/mL). Mean changes in CD4 cell counts and log<sub>10</sub> serum viral RNA are summarised in Figures 2 and 3, respectively. The proportions of patients with serum viral RNA below 500 copies/mL, the limit of quantification of the assay, are summarised in Figure 4.

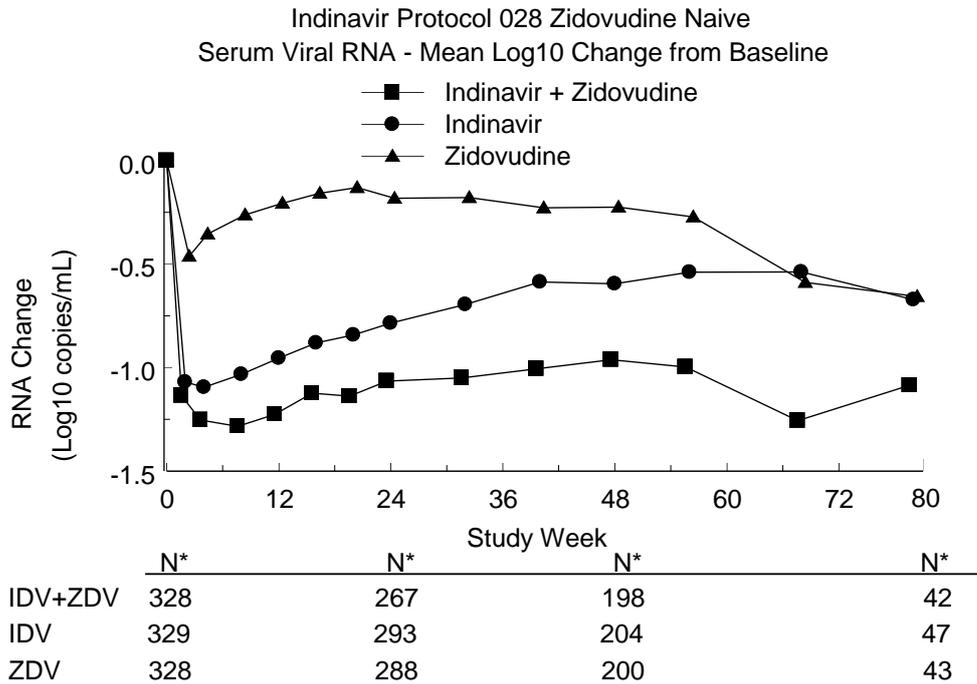
Study 028: Figure 2



\*N=Number with CD4 cell count measurement at Weeks 0, 24, 48, and 80.

Note: Optional addition of lamivudine to zidovudine containing arms at median study week 40 (see text)

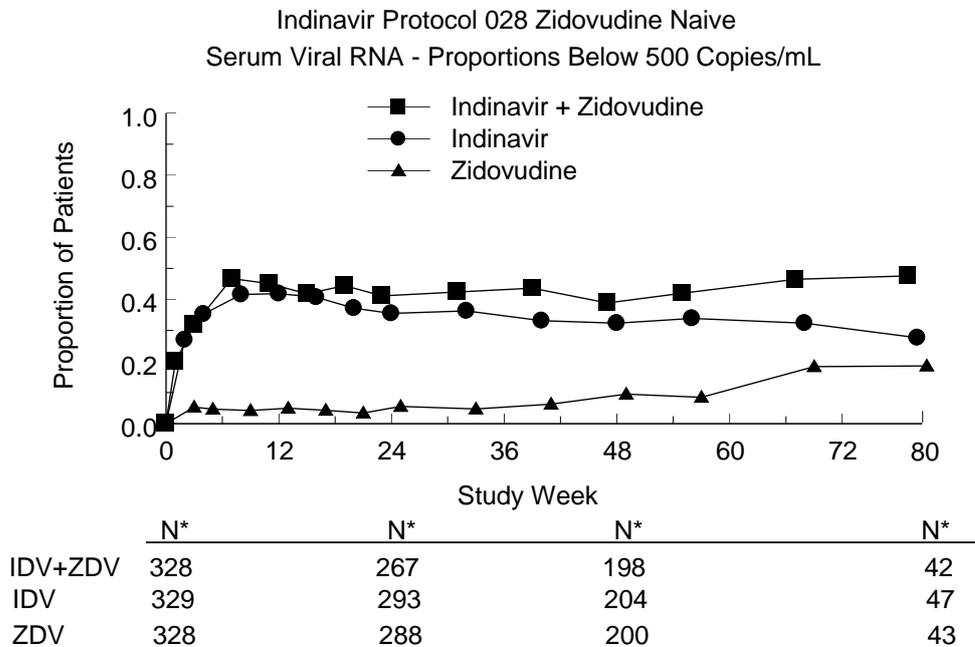
Study 028: Figure 3



\*N=Number with viral RNA measurement at Weeks 0, 24, 48, and 80.

Note: Optional addition of lamivudine to zidovudine containing arms at median study week 40 (see text)

Study 028: Figure 4

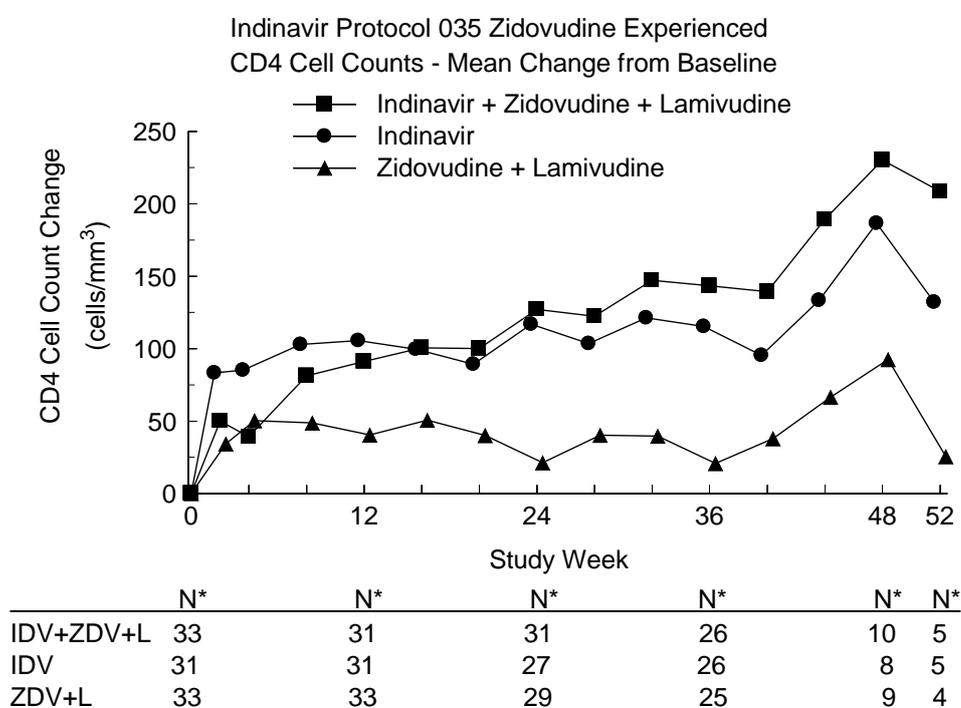


\*N=Number with viral RNA measurement at Weeks 0, 24, 48, and 80.

Note: Optional addition of lamivudine to zidovudine containing arms at median study week 40 (see text)

Study 035 is a multicentre, randomised, surrogate marker trial comparing the effects of CRIXIVAN with those of CRIXIVAN plus zidovudine plus lamivudine and those of zidovudine plus lamivudine on CD4 cell counts and serum viral RNA. All patients were required to be protease-inhibitor and lamivudine naive, and zidovudine experienced, with CD4 cell counts between 50 and 400 cells/mm<sup>3</sup> and serum viral RNA levels  $\geq 20,000$  copies/mL. The study enrolled 97 HIV-1 seropositive patients (15% female, 12% Hispanic/Latin American, 10% Black, 4% Asian/Other, median age 40 years, median time of prior zidovudine therapy 29.7 months). Treatment was changed to open label therapy with CRIXIVAN plus zidovudine plus lamivudine after at least 24 weeks of double-blind, randomised therapy. The median length of double-blind follow-up was 41 weeks with a maximum of 52 weeks. The mean baseline CD4 cell count over all patients was 175 cells/mm<sup>3</sup>, and the mean baseline serum viral RNA was 4.62 log<sub>10</sub> copies/mL (41,230 copies/mL). Mean changes in CD4 cell counts and log<sub>10</sub> serum viral RNA during the double-blind portion are summarised in Figures 5 and 6, respectively. The proportions of patients during the double-blind portion with serum viral RNA below 500 copies/mL, the limit of quantification of the assay, are summarised in Figure 7.

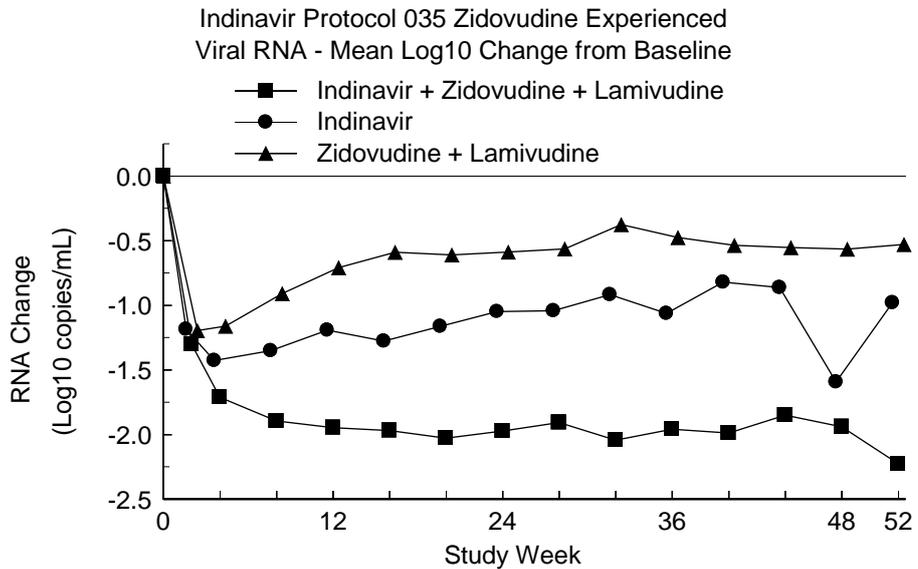
Study 035: Figure 5



\*N = Number during double-blind portion with CD4 cell count measurement at Weeks 0, 12, 24, 36, 48, 52

N decreases after Week 24 due to variable lengths of double-blind follow-up (see text).

Study 035: Figure 6

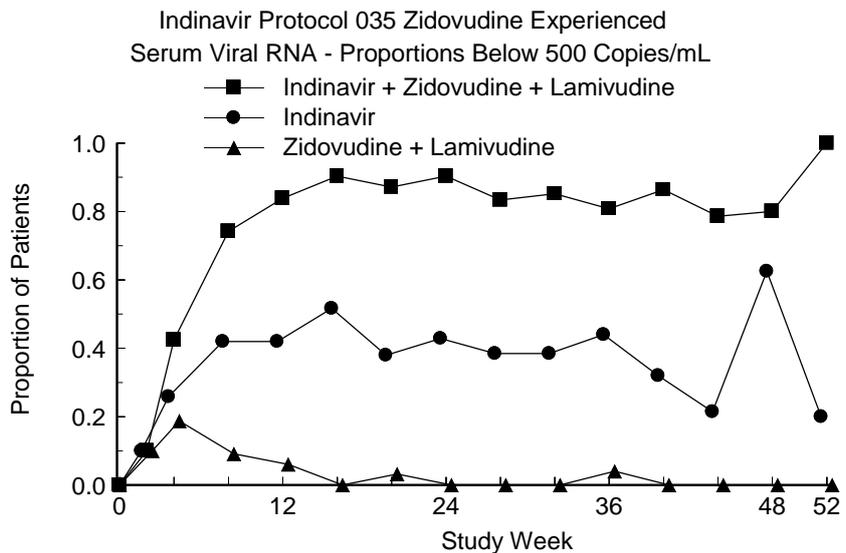


	N*	N*	N*	N*	N*	N*
IDV+ZDV+L	32	30	30	25	10	5
IDV	31	31	28	25	8	5
ZDV+L	33	33	30	25	9	5

\*N = Number during double-blind portion with RNA measurement at Weeks 0, 12, 24, 36, 48, 52

N decreases after Week 24 due to variable lengths of double-blind follow-up (see text).

Study 035: Figure 7



	N*	N*	N*	N*	N*	N*
IDV+ZDV+L	33	31	31	26	10	5
IDV	31	31	28	25	8	5
ZDV+L	33	33	30	25	9	5

\*N = Number during double-blind portion with RNA measurement at Weeks 0, 12, 24, 36, 48, 52

N decreases after Week 24 due to variable lengths of double-blind follow-up (see text).

### *Paediatric Patients*

Study 068 is an open-label, multicentre study conducted to evaluate the safety, antiretroviral activity and pharmacokinetics of indinavir at a dose of 500 mg/m<sup>2</sup> every 8 hours, in combination with stavudine and lamivudine in HIV-infected paediatric patients. All patients were required to be protease inhibitor naive and naive to at least one of the reverse transcriptase inhibitors, stavudine or lamivudine. The study enrolled 25 HIV-1 seropositive patients (68% female, 28% Caucasian, 68% Black, 4% Hispanic/Latin American) aged 4 to 15 years who were able to swallow capsules. The mean baseline plasma viral RNA was 4.00 log<sub>10</sub> copies/mL; the mean baseline CD4 cell count was 594 cells/mm<sup>3</sup>; and the mean baseline percent CD4 cell count was 26%. At Week 24, the percentage of patients (n=23) with plasma viral RNA below 400 copies/mL; the lower limit of quantification of the assay, was 60%; the mean increase in CD4 cell counts was 242 cells/mm<sup>3</sup>; and the mean increase in percent CD4 cell counts was 4.2%.

Study ACTG 395 is an open-label, multicentre study identical in design to Study 068. The study enrolled 16 HIV-1 seropositive patients (38% female, 6% Caucasian, 63% Black, 31% Hispanic/Latin American) aged 5 to 13 years who were able to swallow capsules. The mean baseline plasma viral RNA was 3.89 log<sub>10</sub> copies/mL; the mean baseline CD4 cell count was 678 cells/mm<sup>3</sup>; and the mean baseline percent CD4 cell count was 30%. At Week 16, the percentage of patients (n=11) with plasma viral RNA below 400 copies/mL was 59%; the mean increase in CD4 cell counts was 73 cells/mm<sup>3</sup>; and the mean increase in percent CD4 cell counts was 1.2%.

## **INDICATIONS**

CRIXIVAN (Indinavir sulfate) is indicated for the treatment of adults with HIV-1 infection.

CRIXIVAN should be used in combination therapy with other appropriate antiretroviral agents.

## **CONTRAINDICATIONS**

CRIXIVAN (Indinavir sulfate) is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Indinavir should not be administered concurrently with drugs with narrow therapeutic windows and which are substrates of CYP3A4. Co-administration with amiodarone, terfenadine, astemizole, cisapride, alprazolam, triazolam, midazolam, pimozide, ergot derivatives, lovastatin, or simvastatin may result in competitive inhibition of the metabolism of these drugs and create the potential for serious and or life-threatening adverse events such as cardiac arrhythmias (e.g., terfenadine, astemizole cisapride), prolonged sedation or respiratory depression (e.g., alprazolam, triazolam, midazolam), vasospastic reactions (ergot derivatives), myopathy including rhabdomyolysis (lovastatin or simavstatin).

## **PRECAUTIONS**

### **Nephrolithiasis/Urolithiasis**

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN therapy. The cumulative frequency of nephrolithiasis is substantially higher in paediatric and adolescent 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 haematuria or microscopic haematuria), temporary interruption (eg., 1-3 days) or discontinuation of therapy may be considered. Adequate hydration is recommended in all patients treated with CRIXIVAN. (See ADVERSE EFFECTS and DOSAGE AND ADMINISTRATION, Nephrolithiasis).

During post-marketing surveillance of patients treated with indinavir, rare reports of interstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leukocyturia (>100 cells/high power field). In patients with asymptomatic severe leukocyturia, further evaluation may be warranted.

#### Hyperbilirubinaemia

Indirect hyperbilirubinaemia has occurred frequently during treatment with indinavir and has infrequently been associated with increases in serum transaminases (see ADVERSE REACTIONS). It is not known whether indinavir will exacerbate the physiologic hyperbilirubinaemia seen in neonates (see PRECAUTIONS, USE IN PREGNANCY).  
Hepatic impairment

Mild to moderate hepatic impairment due to cirrhosis increases the AUC and half-life of indinavir. Dosage reduction is recommended (see PHARMACOLOGY; DOSAGE AND ADMINISTRATION). Patients with severe hepatic insufficiency have not been studied.

#### Hepatitis

Hepatitis including rare cases of hepatic failure have 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.

#### Acute Haemolytic anaemia

Acute haemolytic anaemia has been reported which in some cases was severe and progressed rapidly. Once a diagnosis is apparent, appropriate measures for the treatment of haemolytic anaemia should be instituted which may include discontinuation of CRIXIVAN. (see ADVERSE REACTIONS)

#### Hyperglycaemia

There have been reports of new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus occurring in HIV-infected patients receiving protease inhibitor therapy. Many of these reports occurred in patients with confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred.

In the majority of cases, treatment with protease inhibitors was continued while in some cases treatment was either discontinued or interrupted. In some patients, hyperglycaemia persisted after the protease inhibitor was withdrawn, whether or not diabetes was reported at baseline.

#### Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including CRIXIVAN. During the initial phase of treatment, a patient whose immune system responds to CART may mount an inflammatory response to

indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

#### Drug Interactions

Concomitant use of CRIXIVAN with lovastatin or simvastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis. Based on an interaction study with lopinavir/ritonavir, combination of rosuvastatin and protease inhibitors is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with atorvastatin. The interaction of CRIXIVAN with pravastatin or 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 drugs.

Coadministration of CRIXIVAN and drugs primarily metabolised by CYP3A4 may result in increased plasma concentrations of the other drug with the potential for increased toxicity. Caution should be exercised during concomitant use of CRIXIVAN with quetiapine. If coadministration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions as recommended in the quetiapine prescribing information.

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 and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

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.

#### Body fat changes

Redistribution or accumulation of body fat including central obesity, dorsocervical fat enlargement and breast enlargement and loss of body fat from the face, limbs and upper trunk (peripheral lipodystrophy) have been reported in HIV positive patients taking protease inhibitors. Some of these patients had hyperglyceridaemia and insulin resistance also. The long term implications of these changes are not known.

#### Patients with Coexisting Conditions

There have been reports of spontaneous bleeding in patients with haemophilia 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.

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN (See ADVERSE REACTIONS).

## Absorption

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

## Information for Patients

Indinavir is not a cure for HIV infection and patients may continue to develop opportunistic infections and other complications associated with HIV disease. Indinavir has not been shown to reduce the incidence or frequency of such illnesses. Patients should be advised to remain under the care of a physician when using indinavir and should not modify or discontinue treatment without first consulting the physician. Therefore, therapy with indinavir should be initiated and maintained at the recommended dosage. If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double this dose.

The long term effects of indinavir when taken alone or in combination therapy are unknown at this time. Indinavir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

CRIVAN 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.

## **Carcinogenicity/Mutagenicity and Impairment of Fertility**

Data on the carcinogenicity of indinavir are not yet available.

Indinavir, with or without metabolic activation as appropriate, was not mutagenic in assays for gene mutations (*in vivo* microbial and mammalian cell mutagenesis assays), chromosome damage (*in vitro* and *in vivo* chromosomal aberration assays) and DNA damage (*in vitro* alkaline elution assay).

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 up to 640 mg/kg/day. This dose provides 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.

## **Use in Pregnancy (Category B3)**

Reproduction studies conducted with indinavir in rats and rabbits at maternal exposures (based on AUC values) comparable to, or slightly greater than, human exposure revealed no evidence of teratogenicity. No treatment-related external or visceral changes were observed in rats, but there were treatment-related increases over controls in the incidence of supernumerary ribs and of cervical ribs at exposures at or below those in humans. No treatment-related external, visceral or, skeletal changes were seen in rabbits, but foetal exposure was low in this species compared with the rat. In both rats and rabbits, there were no treatment-related effects on embryonic/foetal survival or foetal weights.

Hyperbilirubinaemia has occurred in some patients during treatment with indinavir. It is not known whether the drug will exacerbate physiological hyperbilirubinaemia in neonates.

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

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 available in this patient population, use of indinavir is not recommended in HIV-infected pregnant patients ( see PHARMACOLOGY, *pregnant patients*).

### **Use in Lactation**

It is not known whether indinavir is excreted in human milk. The drug was excreted in the milk of rats and caused significant decreases in body-weight gain of the pups at daily maternal exposures (based on AUC) estimated to be about half of those in humans. Because many drugs are excreted in human milk, and because of the potential for adverse reactions to indinavir in nursing infants, breast feeding should be stopped during treatment with indinavir.

### **Use in Children**

CRIXIVAN has not been evaluated in children below 3 years of age. For currently available data in children 3 years of age and older, see ADVERSE EFFECTS and PHARMACOLOGY; under "Paediatric Patients".

### **Use in Elderly**

Safety and effectiveness in elderly patients have not been established.

## **INTERACTIONS WITH OTHER DRUGS**

Specific drug interaction studies were performed with indinavir and the following drugs including: zidovudine, zidovudine/lamivudine, stavudine, trimethoprim/sulfamethoxazole, fluconazole, clarithromycin, methadone or an oral contraceptive (ethinyl oestradiol/norethindrone 1/35).

No clinically significant interactions were observed with these drugs.

However, in these studies, the dose of clarithromycin tested was 500 mg twice daily and the dose of trimethoprim tested (as part of double strength trimethoprim and sulfamethoxazole) was 160 mg twice daily. It is not known if a clinically significant drug interaction would result if indinavir was coadministered with substantially higher doses of these drugs.

When isoniazid was given in combination with indinavir, the pharmacokinetic parameters of indinavir were not altered. The AUC and  $C_{max}$  of isoniazid were increased - mean values 1.12 and 1.34 times respectively. It is not clear whether these changes affect the clinical adverse effects profile of isoniazid.

The effects of chronic alcohol ingestion on indinavir metabolism have not been studied.

Clinically significant interactions with other drugs are described below.

#### **Rifabutin**

The coadministration of indinavir 800mg every eight hours with rifabutin either 300mg once daily or 150mg once daily was evaluated in two separate clinical studies. The results of

these studies showed a decrease in indinavir AUC (34% and 33%, respectively, versus indinavir 800mg every eight hours alone) and an increase in rifabutin AUC (173% and 55%, respectively, versus rifabutin 300mg once daily alone). (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Rifabutin). This increase in rifabutin plasma concentrations is likely related to inhibition of CYP3A4 - mediated metabolism of rifabutin by indinavir. A dosage increase of indinavir and a dosage reduction of rifabutin are necessary when CRIXIVAN and rifabutin are co-administered.

#### Pimozide

Pimozide should not be used together with indinavir. Inhibition of CYP3A4 by indinavir could result in elevated plasma concentrations of pimozide which could potentially result in QT prolongation and associated ventricular arrhythmias (see CONTRAINDICATIONS).

#### Ketoconazole

Administration of indinavir 600 mg tds with ketoconazole 400 mg daily resulted in a 20% reduction in AUC<sub>0-8 hr</sub> and 31% reduction in C<sub>max</sub> for indinavir compared to indinavir 800mg tds alone. A dosage reduction of indinavir to 600 mg every 8 hours should be considered when indinavir and ketoconazole are coadministered. (See DOSAGE AND ADMINISTRATION).

#### Itraconazole

Indinavir 600mg tds given with itraconazole 200mg bd resulted in a 1% reduction in AUC<sub>0-8 hr</sub> and 22% reduction in C<sub>max</sub> for indinavir compared to indinavir 800mg tds alone. A dosage reduction of indinavir to 600mg every 8 hours is recommended when CRIXIVAN and itraconazole are coadministered. (See DOSAGE AND ADMINISTRATION)

#### Delavirdine

Single doses of indinavir 600mg had no effect on the pharmacokinetics of delavirdine. Delavirdine 400mg tds given with single 400mg and 600mg doses of indinavir resulted in AUCs which were 86% and 144% respectively of the AUC for a single 800mg dose of indinavir given alone. The effect of delavirdine on a single 800mg dose of indinavir has not been studied. Based on the limited data available, a dosage reduction of indinavir to 600 mg every 8 hours should be considered when CRIXIVAN and delavirdine are coadministered. (See DOSAGE AND ADMINISTRATION)

#### Efavirenz

The optimal dose of indinavir, when given in combination with efavirenz, is not known.

#### 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.

#### Rifampicin

Administration of indinavir (800mg every eight hours) with rifampicin (600mg once daily) for one week resulted in an 89% ± 9% decrease in indinavir AUC. Rifampicin is a potent inducer of P450 3A4 which markedly diminishes plasma concentrations of indinavir. Therefore, CRIXIVAN and rifampicin should not be co-administered.

#### Ritonavir

Ritonavir increases indinavir plasma concentrations; indinavir may affect ritonavir plasma concentrations. Currently, there are no safety or efficacy data available on the use of this combination in patients. In cases of co-administration of ritonavir and indinavir (dosed at 800 mg twice daily), caution is warranted as the risk of nephrolithiasis can be increased. Appropriate hydration is highly recommended. If the indinavir dose is reduced due to tolerability problems, plasma drug monitoring may be valuable. There is insufficient data

available to support a definitive relationship between indinavir plasma levels and efficacy and the occurrence of nephrolithiasis.

#### HMG-CoA Reductase Inhibitors

Concomitant use of CRIXIVAN with lovastatin or simvastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis. Based on an interaction study with lopinavir/ritonavir, combination of rosuvastatin and protease inhibitors is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with atorvastatin. The interaction of CRIXIVAN with pravastatin or 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 drugs.

#### St. John's Wort (*Hypericum perforatum*)

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 and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

#### Venlafaxine

Venlafaxine decreases indinavir plasma concentrations. Indinavir did not affect the plasma concentrations of venlafaxine and active metabolite O-desmethyl-venlafaxine. The clinical significance of this finding is unknown.

#### Drugs Metabolized by CYP3A4

Coadministration of CRIXIVAN a CYP3A4 inhibitor, with calcium channel blockers and other drugs metabolized by CYP3A4 may result in increased plasma concentrations of these drugs which could increase or prolong their therapeutic and adverse effects (see PRECAUTIONS).

Consideration should be given to the possibility of interactions with other drugs that are metabolised by or inhibit the CYP3A4 enzyme, including erythromycin and serotonin - reuptake inhibitor antidepressant drugs such as sertraline, fluoxetine and fluvoxamine.

#### Midazolam

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).

Other drugs that induce CYP3A4 less potently than rifampicin, such as phenobarbitone, phenytoin, carbamazepine and dexamethasone should be used cautiously together with indinavir since they could also diminish plasma concentrations of indinavir.

#### PDE5 Inhibitors

Coadministration of CRIXIVAN with sildenafil, tadalafil, or vardenafil (PDE5 inhibitors) is expected to substantially increase the plasma concentrations of these compounds and may result in an increase in PDE5 inhibitor -associated adverse events, including hypotension, visual changes, and priapism (see the manufacturer's complete prescribing information for sildenafil, tadalafil, or vardenafil for recommended dosage adjustments.)

### Didanosine

A formal drug interaction study between indinavir and didanosine has not been performed. However, a normal (acidic) gastric pH may be necessary for optimum absorption of indinavir whereas acid rapidly degrades didanosine which is formulated with buffering agents to increase pH. Indinavir and didanosine should be administered at least one hour apart on an empty stomach (consult the manufacturer's prescribing information for didanosine). Antiretroviral activity was unaltered when didanosine was administered three hours after treatment with indinavir in one clinical study.

### Grapefruit juice

The administration of indinavir with grapefruit juice resulted in significant decreases in indinavir AUC ( $26 \pm 17\%$ ) and  $C_{max}$  ( $33 \pm 22\%$ ). Therefore, the concomitant use of grapefruit juice and indinavir should be avoided.

## ADVERSE EFFECTS

### Clinical Trial Data

Drug-related clinical adverse experiences of moderate or severe intensity in  $\geq 2\%$  of patients treated with indinavir alone, indinavir in combination with zidovudine, or zidovudine alone are presented in Table 1. Adverse event profiles reported in patients who received indinavir in other clinical trials were generally similar to those reported below in Table 1.

Table 1  
Drug-Related Clinical Adverse Experiences of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Patients  
Studies 028 and 033\*

Adverse Experience	Indinavir Percent (n=196)	Indinavir plus zidovudine Percent (n=196)	Zidovudine Percent (n=195)
<i>Body as a Whole</i>			
Abdominal pain	8.7	8.2	5.1
Asthenia/fatigue	3.6	9.2	7.7
Flank pain	2.6	1.0	0
Malaise	0.5	2.0	1.5
<i>Digestive System</i>			
Nausea	11.7	32.1	14.4
Diarrhoea	4.6	4.1	2.1
Vomiting	4.1	12.2	4.6
Acid regurgitation	2.0	2.0	0.5
Anorexia	0.5	2.0	3.1
Dry mouth	0.5	0	2.1
<i>Musculoskeletal System</i>			
Back pain	2.0	1.0	1.5
<i>Nervous System/Psychiatric</i>			
Headache	5.6	11.7	5.1
Insomnia	3.1	1.5	0
Dizziness	1.0	3.6	0.5
Somnolence	1.0	1.5	3.6
<i>Special Senses</i>			
Taste perversion	2.6	3.6	2.1

\* In Study 033, antiretroviral naïve HIV+ adult subjects received indinavir, zidovudine or indinavir + zidovudine

Oedema/swelling, weight gain and alopecia of moderate to severe intensity occurred in <2% of the patients receiving indinavir.

**In clinical trials with indinavir given at the recommended dose, nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), has been reported in 9.8%(252/2577) of patients receiving indinavir (alone or in combination with other antiretroviral agents) compared to 2.2% in the control arms. In general, these events were not associated with renal dysfunction and resolved with hydration and temporary interruption of therapy (e.g., 1-3 days). (See PRECAUTIONS: nephrolithiasis, and DOSAGE AND ADMINISTRATION).**

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

Adverse events occurring in less than 2% of patients receiving indinavir in all Phase II/Phase III studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate intensity are listed below by body system.

*Body As A Whole/Site Unspecified:* Abdominal distension, chest pain, chills, fever, flank pain, flu-like illness, fungal infection, malaise, pain, syncope.

*Cardiovascular System:* Cardiovascular disorder, palpitation.

*Digestive System:* Acid regurgitation, anorexia, aphthous stomatitis, cheilitis, cholecystitis, cholestasis, constipation, dry mouth, dyspepsia, eructation, flatulence, gastritis, gingivitis, glossodynia, gingival haemorrhage, increased appetite, infectious gastroenteritis, jaundice, liver cirrhosis.

*Haemic and Lymphatic System:* Anaemia, lymphadenopathy, spleen disorder. A few cases of bleeding episodes in HIV-1 positive patients with haemophilia have been reported with indinavir and other protease inhibitors. There is no conclusive evidence, however, to establish that indinavir is a cause of these bleeding episodes.

*Metabolic/Nutritional/Immune:* Food allergy.

*Musculoskeletal System:* Arthralgia, back pain, leg pain, myalgia, muscle cramps, muscle weakness, musculoskeletal pain, shoulder pain, stiffness.

*Nervous System and Psychiatric:* Agitation, anxiety, anxiety disorder, bruxism, decreased mental acuity, depression, dizziness, dream abnormality, dysaesthesia, excitement, fasciculation, hypoaesthesia, nervousness, neuralgia, neurotic disorder, paraesthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo.

*Respiratory System:* Cough, dyspnoea, halitosis, pharyngeal hyperaemia, pharyngitis, pneumonia, rales/rhonchi, respiratory failure, sinus disorder, sinusitis, upper respiratory infection.

*Skin and Skin Appendage:* Body odour, contact dermatitis, dermatitis, dry skin, flushing, folliculitis, herpes simplex, herpes zoster, night sweats, pruritus, seborrhoea, skin disorder, skin infection, sweating, urticaria.

*Special Senses:* Accommodation disorder, blurred vision, eye pain, eye swelling, orbital oedema, taste disorder.

*Urogenital System:* Dysuria, haematuria, hydronephrosis, nocturia, premenstrual syndrome, proteinuria, renal colic, urinary frequency, urinary tract infection, urine abnormality, urine sediment abnormality, urolithiasis.

CRIXIVAN did not alter the type, frequency, or severity of known major toxicities associated with the use of zidovudine, didanosine, or lamivudine.

### Post-Marketed Experience

The following additional adverse experiences have been reported in post-marketed experience without regard to causality:

*Body as a Whole/Site Unspecified:* abdominal distension; redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen, and retroperitoneum.

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

*Digestive System:* liver function abnormalities; hepatitis including rare reports of hepatic failure (see PRECAUTIONS).

*Endocrine/Metabolic:* new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus (see PRECAUTIONS); pancreatitis.

*Haematologic:* increased spontaneous bleeding in patients with haemophilia (see PRECAUTIONS); thrombocytopenia; anaemia including acute haemolytic anaemia.

*Hypersensitivity,* anaphylactoid reactions; vasculitis.

*Musculoskeletal System:* peri-arthritis

*Nervous System/Psychiatric:* oral paraesthesia

*Skin and Skin Appendage:* rash including erythema multiforme and Stevens Johnson Syndrome; hyperpigmentation; alopecia; urticaria; ingrown toenails and/or paronychia.

*Urogenital System:* nephrolithiasis, generally without renal dysfunction; however, there have been reports of nephrolithiasis with renal dysfunction including acute renal failure (see PRECAUTIONS); pyelonephritis; renal insufficiency; renal failure leukocyturia; crystalluria; interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of CRIXIVAN.

### **Laboratory Test Findings**

Asymptomatic hyperbilirubinaemia (total bilirubin  $\geq 43 \mu\text{mol/L}$ ), reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has occurred in approximately 10% of patients treated with indinavir alone or in combination with other antiretroviral agents. Most patients continued treatment with indinavir without dosage reduction and bilirubin values gradually declined toward baseline. Hyperbilirubinaemia occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

Table 2  
Selected Laboratory Abnormalities Reported in Studies 028 and 033\*\*

Adverse Experience	Indinavir Percent (n=196)	Indinavir plus zidovudine Percent (n=196)	Zidovudine Percent (n=195)
<i>Haematology</i>			
Decreased haemoglobin <8.0g/dL	0.5	1.1	0.5
Decreased platelet count <50 THS/mm <sup>3</sup>	0.5	0.5	0
Decreased neutrophils <0.75 THS mm <sup>3</sup>	1.1	1.6	3.8
<i>Blood chemistry</i>			
Increased ALT >500% ULN*	3.1	3.2	2.1
Increased AST >500% ULN	2.1	2.1	1.1
Total serum bilirubin>2.5 mg/dL	7.8	7.4	0.5
Increased serum amylase> 200% ULN	1.0	2.1	0.5

\*Upper limit of the normal range

\*\* In Study 033, antiretroviral naïve HIV+ adult subjects received indinavir, zidovudine or indinavir + zidovudine

### Paediatric Population

In clinical trials in paediatric patients 3 years of age and older, the adverse experience profile was similar to that for adult patients except for a higher frequency of nephrolithiasis which is substantially higher in paediatric patients (29%) than in adult patients (12.4%), who were treated with indinavir at a dose of 500 mg/m<sup>2</sup> every 8 hours. In clinical trials with indinavir, asymptomatic pyuria of unknown aetiology was noted in 10.9% (6/55) of paediatric patients 3 years of age and older who received indinavir at a dose of 500 mg/m<sup>2</sup> every 8 hours. Some of these events were associated with mild elevation of serum creatinine.

### Post-Marketed Experience

The following additional laboratory adverse experiences have been reported:

Increased serum triglycerides; increased serum cholesterol.

## DOSAGE AND ADMINISTRATION

The capsules should be swallowed whole.

The recommended dosage of CRIXIVAN is 800mg orally every 8 hours. Therapy with CRIXIVAN **must be initiated at the recommended dose of 2.4 g/day** (see Drug Resistance).

Adequate hydration must be ensured to help minimise the risk of nephrolithiasis. It is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours. Grapefruit juice should be avoided as it reduces the plasma concentration of indinavir (see Absorption). In addition to adequate hydration, medical management in patients with one or more episodes of nephrolithiasis may include temporary interruption of therapy (e.g., 1 to 3 days) during the acute episode of nephrolithiasis or discontinuation of therapy.

Since CRIXIVAN must be taken at intervals of 8 hours, a schedule convenient for the patient should be developed. 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 a light meal, e.g., dry toast with jam, apple juice, and coffee with skim milk and sugar or corn flakes, skim milk and sugar. Administration with a light meal results in slightly increased variability in the

absorption of indinavir. High fat/ high protein/ high calorie meals will substantially decrease the absorption of indinavir.

CRIXIVAN should be used in combination therapy with other appropriate agents.

When other drugs are taken in combination with indinavir, the doses of each drug in relation to food should be based on the information in the product information documents for each drug. In some instances it will be necessary for patients to take some drugs (including CRIXIVAN) before meals and other drugs after the same meals.

### Concomitant Therapy

#### Rifabutin

Dose reduction of rifabutin to half the standard dose is recommended (consult the manufacturer's prescribing information) and a dose increase of CRIXIVAN to 1000 mg every eight hours are recommended when rifabutin and CRIXIVAN are co-administered (see Interactions with Other Drugs).

#### Ketoconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering ketoconazole concurrently (see Interactions with Other Drugs).

#### Itraconazole

Dose reduction of CRIXIVAN 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently (see Interactions with Other Drugs).

#### Delavirdine

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day (see Interactions with Other Drugs).

#### Efavirenz

The optimal dose of indinavir, when given in combination with efavirenz, is not known.

### Special Populations

#### Paediatric Patients

The optimal dosing regimen for use of indinavir in paediatric patients has not been established. A dose of 500 mg/m<sup>2</sup> every eight hours has been studied in uncontrolled studies of small number of children, 3 years and older. The pharmacokinetic parameter C<sub>8h</sub> (trough) of indinavir at this dose was not comparable to profiles previously observed in adults receiving the recommended dose (see PHARMACOLOGY). Physicians considering the use of indinavir in paediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis (see PRECAUTIONS and ADVERSE EFFECTS).

#### Hepatic Insufficiency

Based on limited pharmacokinetic data the dosage of CRIXIVAN should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis (see Precautions - hepatic impairment).

#### Nephrolithiasis

Adequate hydration must be ensured to help minimise the risk of nephrolithiasis (see above). In addition to adequate hydration, medical management in patients who experience nephrolithiasis may include temporary interruption of therapy (e.g., 1-3 days) during the acute episode of nephrolithiasis or discontinuation of therapy.

## **OVERDOSAGE**

There have been reports of human overdosage with CRIXIVAN. The most commonly reported symptoms were gastrointestinal (eg., nausea, vomiting, diarrhoea) and renal (eg., nephrolithiasis, flank pain, haematuria). It is not known whether indinavir is dialysable by peritoneal or haemodialysis.

## **PRESENTATION AND STORAGE CONDITIONS**

**CRIXIVAN 200mg**, semi-translucent white capsule coded CRIXIVAN™ 200mg in blue. Available in bottles.

**CRIXIVAN 400mg**, semi-translucent white capsule coded CRIXIVAN™ 400mg in green. Available in bottles.

CRIXIVAN Capsules are sensitive to moisture. CRIXIVAN should be dispensed and stored in the original container. Store below 30°C.

For bottles, the desiccant should remain in the original container.

## **NAME AND ADDRESS OF THE SPONSOR**

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED  
LEVEL 1, BUILDING A, 26 TALAVERA ROAD  
MACQUARIE PARK NSW 2113

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (Schedule 4)

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

6 March 1998

## **DATE OF MOST RECENT AMENDMENT**

6 July 2015