

PRODUCT MONOGRAPH

PrCRIXIVAN[®]

indinavir sulfate capsules

100, 200, 300, and 400 mg

(as indinavir)

HIV Protease Inhibitor

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CRIXIVAN[®]

indinavir sulfate capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsules 100 mg , 200 mg, 300 mg, 400 mg as indinavir	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

CRIXIVAN[®] (indinavir sulfate) in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Clinical studies with indinavir sulfate in adults demonstrated:

- reduced risk of progression to an AIDS-defining illness or death;
- durable reduction in serum viral RNA;
- durable increase in CD4 cell counts.

CONTRAINDICATIONS

- CRIXIVAN[®] (indinavir sulfate) is contraindicated in patients with clinically significant hypersensitivity to any of its ingredients. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Co-administration of indinavir sulfate is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (i.e. cardiac arrhythmias, prolonged sedation). These drugs are listed in Table 1.

Table 1	
Drugs that are contraindicated with indinavir sulfate	
Drug Class	Drugs Within Class That Are Contraindicated With indinavir sulfate
Antiarrhythmics	amiodarone
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	cisapride (no longer marketed in Canada)
Neuroleptics	pimozide
Sedative/hypnotics	alprazolam, midazolam, triazolam

WARNINGS AND PRECAUTIONS

Coadministration of CRIXIVAN[®], a CYP3A4 inhibitor, with calcium channel blockers, trazodone 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.

The potential exists for interaction between indinavir sulfate and other P450 (CYP3A4) substrates which have not been studied (see CONTRAINDICATIONS – Table 1, DRUG INTERACTIONS, and ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics).

Endocrine and Metabolism

Hyperglycemia

There have been reports of new onset diabetes mellitus or hyperglycemia, 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 hyperglycemia. 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 the majority of cases, treatment with protease inhibitors was continued while in some cases treatment was either discontinued or interrupted. In some patients, hyperglycemia persisted after the protease inhibitor was withdrawn, whether or not diabetes was reported at baseline. A causal relationship between protease inhibitor therapy and these events has not been established.

Redistribution/Accumulation of Body Fat

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, facial wasting, 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.

Genitourinary

Nephrolithiasis/Urolithiasis and tubulointerstitial nephritis

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN[®] (indinavir sulfate) therapy in adult and pediatric patients. The cumulative frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (9.8%). The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN[®]; however, the risk over time remains relatively constant. In some cases, nephrolithiasis has been associated with renal insufficiency or acute renal failure. In the majority of these cases, renal insufficiency and acute renal failure were reversible. If signs and symptoms of nephrolithiasis, including flank pain with or without hematuria (including microscopic hematuria), occur, temporary interruption of therapy (e.g., 1-3 days) during the acute episode of nephrolithiasis or discontinuation of therapy may be considered. **Adequate hydration is recommended (at least 1.5 liters a day) in all patients treated with indinavir sulfate (see ADVERSE REACTIONS, Nephrolithiasis/Urolithiasis and DOSAGE AND ADMINISTRATION).**

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). Asymptomatic severe leukocyturia could indicate the presence of renal damage (e.g., tubulointerstitial nephritis) and further evaluation may be warranted. Change in the management of these patients may be necessary to prevent progression of renal damage. The regular use of microscopic urinalyses may add significantly to the safe management of individuals on indinavir treatment.

Hematologic

Hyperbilirubinemia

Indirect hyperbilirubinemia has occurred frequently during treatment with CRIXIVAN[®] (indinavir sulfate) and has infrequently been associated with increases in serum transaminases (see ADVERSE REACTIONS). However, because of the theoretical potential for the compound to exacerbate the physiologic hyperbilirubinemia seen in human neonates, careful consideration must be given to the use of indinavir sulfate in pregnant women at the time of delivery (see Pregnancy).

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 indinavir sulfate.

Bleeding in Hemophiliacs

There have been reports of increased bleeding including spontaneous skin hematomas and hemarthrosis in patients with Hemophilia Type A and Type B treated with protease inhibitors. In some patients, additional Factor VIII was given. In many of the reported cases, treatment with protease inhibitors was continued or re-introduced. There is no proven relationship between protease inhibitors and such bleeding, however, the frequency of bleeding episodes should be closely monitored in patients on indinavir sulfate.

Hepatic/Biliary/Pancreatic

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.

Patients with Hepatic Insufficiency due to Cirrhosis

In these patients, the dosage of indinavir sulfate should be lowered because of decreased metabolism of the drug (see DOSAGE AND ADMINISTRATION and DETAILED PHARMACOLOGY - Pharmacokinetics, Hepatic Insufficiency Due to Cirrhosis).

Immune

Immune Reconstitution

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Neurologic

CNS penetration of indinavir sulfate has not been established.

Renal

Patients with renal insufficiency have not been studied.

Drug Interactions (see DRUG INTERACTIONS)

HMG-CoA Reductase Inhibitors (statins)

HMG-CoA reductase inhibitors (statins) may interact with protease inhibitors and increase the risk of myopathy, including rhabdomyolysis. Concomitant use of protease inhibitors, including CRIXIVAN[®], with lovastatin or simvastatin is not recommended. Other HMG-CoA reductase inhibitors (statins) may also interact with protease inhibitors. This warning is based on clinical reports, and on indirect evidence from studies on the cytochrome P-450 (CYP3A4) metabolism pathway.

Other Drugs Metabolized by CYP3A4

Coadministration of CRIXIVAN[®], a CYP3A4 inhibitor, with calcium channel blockers, trazodone 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.

Rifampin

Rifampin is a potent inducer of P450 (CYP3A4) which markedly diminishes plasma concentrations of indinavir. Therefore, CRIXIVAN[®] and rifampin should not be coadministered (see DETAILED PHARMACOLOGY, Drug Interactions, Rifampin).

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

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

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 (see DETAILED PHARMACOLOGY, Drug Interactions, St. John's Wort).

Sildenafil

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including indinavir. Coadministration of protease inhibitors with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see, DETAILED PHARMACOLOGY, Drug Interactions, Sildenafil, CONSUMER INFORMATION, and the complete prescribing information for sildenafil).

Special Populations

Pregnant Women:

There are no adequate and well controlled studies in pregnant patients. Indinavir sulfate may be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Given substantially lower antepartum exposures that have been observed in a small study of HIV-infected pregnant patients and the limited data in this patient population, indinavir use is not recommended in HIV-infected pregnant patients. (see ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and conditions*, Pregnant Women)

In Rhesus monkeys, administration of indinavir sulfate to neonates caused a mild exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth. Administration of indinavir sulfate to pregnant Rhesus monkeys during the third trimester did not cause a similar exacerbation in neonates; however, only limited placental transfer of indinavir sulfate occurred.

Antiviral 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 910-256-0238 (in the U.S. and Canada, call 1-800-258-4263).

Nursing Women:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse reactions from indinavir sulfate in nursing infants, mothers should be instructed to discontinue nursing if they are receiving indinavir sulfate. In addition, it is advisable for HIV-infected women not to breast-feed to avoid post-natal transmission of HIV to a child who may not be infected.

Pediatrics

A dose of 500 mg/m² every 8 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 of 800 mg every 8 hours (see DETAILED PHARMACOLOGY - Pharmacokinetics). Viral suppression was observed in some of the 21 patients who were followed on a regimen of indinavir 500 mg/m² in combination with D4T and 3TC through 24 weeks. However, a substantially higher rate of nephrolithiasis/urolithiasis was reported when compared to adult historical data (see WARNINGS AND PRECAUTIONS, nephrolithiasis/urolithiasis and tubulointerstitial nephritis). 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.

Geriatrics

Safety and effectiveness in elderly patients have not been established.

ADVERSE REACTIONS

Nephrolithiasis/Urolithiasis

In clinical trials with CRIXIVAN[®] (indinavir sulfate), nephrolithiasis, including flank pain with or without hematuria (including microscopic hematuria), has been reported in approximately 9.8% (252/2577) of patients receiving CRIXIVAN[®] at the recommended dose 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 WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In pediatric patients who were treated with CRIXIVAN[®] at the recommended dose of 500 mg/m² every 8 hours, the cumulative frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (9.8%). The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN[®]; however, the risk over time remains relatively constant.

Hyperbilirubinemia

Asymptomatic hyperbilirubinemia [total bilirubin 42.75 µmol/L (2.5 mg/dL)], reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with indinavir sulfate. In <1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis occurred more frequently at doses exceeding 2.4 g/day.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In controlled clinical trials conducted worldwide, indinavir sulfate was administered alone or in combination with other antiretroviral agents (zidovudine, didanosine, and/or lamivudine) and was found to be generally well tolerated. Indinavir sulfate did not alter the type, frequency, or severity of known major toxicities associated with the use of zidovudine, didanosine, or lamivudine.

Study 028, a double-blind, multicenter, randomized, clinical endpoint trial compared the effects of indinavir sulfate plus zidovudine with those of indinavir sulfate alone or zidovudine alone on the progression to an AIDS-defining illness (ADI) or death, and on surrogate marker responses. The median length of follow-up was 56 weeks with a maximum of 97 weeks (see CLINICAL TRIALS).

Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of indinavir sulfate 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. The median length of follow-up was 38 weeks with a maximum of 52 weeks. (See CLINICAL TRIALS.)

Drug-related clinical adverse reactions of moderate or severe intensity in 2% of patients treated with indinavir sulfate alone, indinavir sulfate in combination with zidovudine, or zidovudine alone are presented in Table 1.

Table 1					
Clinical Adverse Experiences Reported in ≥2% of Patients					
Adverse Experience	Study 028 Considered Drug-Related and of Moderate or Severe Intensity			Study ACTG 320 of Unknown Drug Relationship and of Severe or Life-threatening Intensity	
	CRIXIVAN [®] Percent (n=332)	CRIXIVAN [®] plus Zidovudine Percent (n=332)	Zidovudine Percent (n=332)	CRIXIVAN [®] plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
Body as a Whole					
Abdominal pain	16.6	16.0	12.0	1.9	0.7
Asthenia/fatigue	2.1	4.2	3.6	2.4	4.5
Fever	1.5	1.5	2.1	3.8	3.0
Malaise	2.1	2.7	1.8	0	0
Digestive System					
Nausea	11.7	31.9	19.6	2.8	1.4
Diarrhea	3.3	3.0	2.4	0.9	1.2
Vomiting	8.4	17.8	9.0	1.4	1.4
Acid regurgitation	2.7	5.4	1.8	0.4	0
Anorexia	2.7	5.4	3.0	0.5	0.2
Appetite increase	2.1	1.5	1.2	0	0
Dyspepsia	1.5	2.7	0.9	0	0
Jaundice	1.5	2.1	0.3	0	0
Hemic and Lymphatic System					
Anemia	0.6	1.2	2.1	2.4	3.5
Musculoskeletal System					
Back pain	8.4	4.5	1.5	0.9	0.7
Nervous System/Psychiatric					
Headache	5.4	9.6	6.0	2.4	2.8
Dizziness	3.0	3.9	0.9	0.5	0.7
Somnolence	2.4	3.3	3.3	0	0
Skin and Skin Appendage					
Pruritus	4.2	2.4	1.8	0.5	0
Rash	1.2	0.6	2.4	1.1	0.5
Respiratory System					
Cough	1.5	0.3	0.6	1.6	1.0
Difficulty breathing/ dyspnea/shortness of breath	0	0.6	0.3	1.8	1.0
Urogenital System					
Nephrolithiasis/uroolithiasis*	8.7	7.8	2.1	2.6	0.3
Dysuria	1.5	2.4	0.3	0.4	0.2
Special Senses					
Taste perversion	2.7	8.4	1.2	0.2	0

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

In Phase I and II controlled trials, the following adverse reactions were reported significantly more frequently by those randomized to the arms containing indinavir sulfate than by those

randomized to nucleoside analogues: rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Adverse reactions occurring in less than 2% of patients receiving indinavir sulfate in 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 distention, chest pain, chills, fever, flank pain, flu-like illness, fungal infection, malaise, pain, syncope, redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS, Redistribution/Accumulation of Body Fat).

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 hemorrhage, increased appetite, infectious gastroenteritis, jaundice, liver cirrhosis.

Hemic and Lymphatic System: Anemia, lymphadenopathy, spleen disorder, bleeding in hemophiliacs (see WARNINGS AND PRECAUTIONS).

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, dysesthesia, excitement, fasciculation, hypesthesia, nervousness, neuralgia, neurotic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo.

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

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

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

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

Laboratory Test Abnormalities

The most frequently occurring selected laboratory adverse experiences (incidence, 5%) considered to be possibly, probably, or definitely drug-related by the study investigator in the group treated with indinavir sulfate alone, were changes in ALT, AST, indirect serum bilirubin, total serum bilirubin, and urine protein. Only 1% of patients discontinued treatment due to these laboratory adverse experiences, when treated with indinavir sulfate alone or in combination with other antiretroviral agents. With the exception of hyperbilirubinemia, the incidences of these adverse events with indinavir sulfate monotherapy were lower than in the groups treated with indinavir sulfate in combination with other antiretroviral agents. Similar incidences in drug-related laboratory adverse experiences of changes in ALT, AST, and urine protein were observed in the group treated with zidovudine alone.

In clinical trials with CRIXIVAN[®], asymptomatic pyuria of unknown etiology was noted in 10.9% (6/55) of pediatric patients 3 years of age and older who received CRIXIVAN[®] at the recommended dose of 500 mg/m² every 8 hours. Some of these events were associated with mild elevation of serum creatinine.

Presented in Table 2 are selected laboratory abnormalities reported in patients treated with indinavir sulfate alone, indinavir sulfate in combination with zidovudine, or zidovudine alone in Phase III clinical trials (Studies 028 and 033).

Table 2 Selected Laboratory Abnormalities of Severe or Life-threatening Intensity Reported in Studies 028 and ACTG 320					
	Study 028			Study ACTG 320	
	CRIXIVAN [®] Percent (n=329)	CRIXIVAN [®] plus Zidovudine Percent (n=320)	Zidovudine Percent (n=330)	CRIXIVAN [®] plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
Hematology					
Decreased hemoglobin <7.0 g/dL	0.6	0.9	3.3	2.4	3.5
Decreased platelet count <50 THS/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
Blood chemistry					
Increased ALT >500% ULN*	4.9	4.1	3.0	2.6	2.6
Increased AST >500% ULN	3.7	2.8	2.7	3.3	2.8
Total serum bilirubin >250% ULN	11.9	9.7	0.6	6.1	1.4
Increased serum amylase >200% ULN	2.1	1.9	1.8	0.9	0.3
Increased glucose >250 mg/dL	0.9	0.9	0.6	1.6	1.9
Increased creatinine >300% ULN	0	0	0.6	0.2	0

* Upper limit of the normal range.

Post-Market Adverse Drug Reactions

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

Body As A Whole/Site Unspecified: Redistribution/accumulation of body fat in areas such as the back of the neck, abdomen, and retro-peritoneum (see WARNINGS AND PRECAUTIONS, Redistribution/Accumulation of Body Fat).

Cardiovascular System: Cardiovascular disorders including myocardial infarction and angina pectoris.

Digestive System: Liver function abnormalities, hepatitis including reports of hepatic failure (see WARNINGS AND PRECAUTIONS, Hepatitis); pancreatitis.

Endocrine/Metabolic: New onset diabetes mellitus or hyperglycemia, or exacerbation of pre-existing diabetes mellitus (see WARNINGS AND PRECAUTIONS).

Hematologic: Increased spontaneous bleeding in patients with hemophilia (see WARNINGS AND PRECAUTIONS), thrombocytopenia, anemia including acute hemolytic anemia (see WARNINGS AND PRECAUTIONS).

Hypersensitivity: Angioedema, anaphylaxis, vasculitis.

Nervous System/Psychiatric: oral paresthesia.

Skin and Skin Appendage: Alopecia, hyperpigmentation, urticaria, rash including erythema multiforme and Stevens Johnson syndrome; ingrown toenails and/or paronychia.

Urogenital System: Nephrolithiasis/urolithiasis, generally without renal dysfunction; however, there have been reports of nephrolithiasis/urolithiasis with renal dysfunction including acute renal failure; pyelonephritis; renal insufficiency; leukocyturia; crystalluria; and interstitial nephritis sometimes with indinavir crystal deposits, in some patients, the interstitial nephritis did not resolve following discontinuation of CRIXIVAN[®].

The following additional laboratory experiences have been reported: Increased serum triglycerides; increased serum cholesterol.

DRUG INTERACTIONS

Overview (see CONTRAINDICATIONS section)

Serious Drug Interactions

Indinavir sulfate should not be administered concurrently with the following:

- alprazolam,
- amiodarone,
- cisapride (no longer marketed in Canada),
- ergot derivatives,
- midazolam,
- pimozone,
- triazolam

Competition for P450 (CYP3A4) by indinavir sulfate could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening events (i.e., cardiac arrhythmias, prolonged sedation). The potential exists for interaction between indinavir sulfate and other P450 (CYP3A4) substrates which have not been studied.

Overview

Indinavir is an inhibitor of the cytochrome P450 isoform CYP3A4. Coadministration of CRIXIVAN[®] and a drug 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, WARNINGS AND PRECAUTIONS). 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.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Drugs That Should Not Be Coadministered with CRIXIVAN[®]

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Sedative/hypnotics: midazolam, triazolam, 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. Rifampin is a potent inducer of P450 (CYP3A4) which markedly diminishes plasma concentrations of indinavir sulfate. Therefore, CRIXIVAN [®] and rifampin should not be coadministered (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY, Drug Interactions, Rifampin).

	<p>Specific drug interaction studies were performed with indinavir sulfate and the following drugs: clarithromycin, fluconazole, isoniazid, methadone, norethindrone/ethinyl estradiol 1/35, trimethoprim/sulfamethoxazole, zidovudine, zidovudine/lamivudine. No clinically significant interactions were observed with these drugs.</p>
<p>HMG-CoA Reductase inhibitors: lovastatin, simvastatin</p>	<p>Potential for serious reactions such as risk of myopathy including rhabdomyolysis. Concomitant use of CRIXIVAN[®] with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN[®], are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including CRIXIVAN[®], are used in combination with these drugs (see WARNINGS AND PRECAUTIONS, Drug Interactions, HMG-CoA reductase inhibitors).</p>
<p>Protease inhibitor: atazanavir</p>	<p>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.</p>

Clinically significant interactions were observed with the following drugs:

Concomitant Drug Class: Drug Name	Effect on Concentration of Indinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	↑ indinavir	Due to an increase in indinavir plasma concentrations (preliminary results), a dosage reduction of indinavir should be considered when CRIXIVAN [®] and delavirdine are coadministered (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Delavirdine, DETAILED PHARMACOLOGY, Drug Interactions, Delavirdine).
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓ indinavir	Due to a decrease in the plasma concentration of indinavir, a dosage increase of indinavir is recommended when CRIXIVAN [®] and efavirenz are coadministered. No adjustment of the dose of efavirenz is necessary when given with indinavir (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Efavirenz, DETAILED PHARMACOLOGY, Drug Interactions, Efavirenz).
Nucleoside reverse transcriptase inhibitor: Didanosine	interaction has not been evaluated	When indinavir sulfate and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach.
Other Agents		
Antifungal: Itraconazole	↑ indinavir	Itraconazole is an inhibitor of CYP3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN [®] and itraconazole are coadministered (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Itraconazole, DETAILED PHARMACOLOGY, Drug Interactions,

		Itraconazole).
Antifungal: Ketoconazole	↑ indinavir	Ketoconazole is an inhibitor of CYP3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN [®] and ketoconazole are coadministered (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Ketoconazole, DETAILED PHARMACOLOGY, Drug Interactions, Ketoconazole).
Antidepressant: Venlafaxine	↓ indinavir ↔ 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.
Antimycobacterial: Rifabutin	↓ indinavir ↑ rifabutin	When rifabutin and CRIXIVAN [®] are coadministered, there is an increase in the plasma concentration of rifabutin and a decrease in the plasma concentration of indinavir. A dose reduction of rifabutin and a dose increase of CRIXIVAN [®] are necessary when rifabutin is coadministered with CRIXIVAN [®] . The suggested dose adjustments are expected to result in rifabutin concentrations at least 50% higher than typically observed when rifabutin is administered alone at its usual dose (300 mg/day) and indinavir concentrations which may be slightly less than typically observed when indinavir is administered alone at its usual dose (800 mg every 8 hours) (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Rifabutin, DETAILED PHARMACOLOGY, Drug Interactions, Rifabutin).
PDE5 inhibitor (phosphodiesterase type	↑ sildenafil	Particular caution should be used when prescribing sildenafil in patients receiving

5 inhibitors): Sildenafil		protease inhibitors, including indinavir. Coadministration of protease inhibitors with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY, Drug Interactions, Sildenafil).
Drugs Metabolized by CYP3A	<p>↑ calcium channel blockers</p> <p>↑ trazodone</p> <p>↑ other drugs metabolized by CYP3A4</p>	Coadministration of CRIXIVAN [®] , a CYP3A4 inhibitor, with calcium channel blockers, trazodone 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. The potential exists for interaction between indinavir sulfate and other P450 (CYP3A4) substrates which have not been studied (e.g., mefloquine).
Other drugs that induce CYP3A4	↓ indinavir	Other drugs that induce CYP3A4 less potently than rifampin, such as phenobarbital, phenytoin, carbamazepine, and dexamethasone should be used cautiously together with indinavir sulfate since they could also diminish plasma concentrations of indinavir sulfate.

Drug-Food Interactions

Ingestion of CRIXIVAN[®] with a meal high in calories, fat, and protein reduces the absorption of CRIXIVAN[®]. For optimal absorption, CRIXIVAN[®] should be administered without food but with water 1 hour before or 2 hours after a meal. (See DOSAGE AND ADMINISTRATION).

Drug-Herb Interactions

St. John's wort (*Hypericum perforatum*)

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 (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY, Drug Interactions, St. John's Wort (*Hypericum perforatum*)).

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults:

The recommended dosage of CRIXIVAN[®] (indinavir sulfate) is 800 mg orally every 8 hours.

Therapy with INDINAVIR SULFATE MUST BE INITIATED at the recommended dose of 2.4 g/day.

Pediatric Patients (3 years of age and older who are able to swallow capsules):

The optimal dosing regimen of indinavir in pediatric patients has not been established. A dose of 500 mg/m² (dose adjusted from calculated body surface area, table of formula below) every 8 hours in combination with 2 nucleoside reverse transcriptase inhibitors has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. Viral suppression below the limit of quantitation was observed in 60% of the 21 pediatric patients who were followed on this regimen through 24 weeks. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adult patients receiving the recommended dose (see DETAILED PHARMACOLOGY - Pharmacokinetics -Absorption in Pediatric Patients). This dose should not exceed the adult dose of 800 mg every 8 hours. CRIXIVAN[®] has not been studied in children under 3 years of age.

Pediatric Dose of CRIXIVAN[®] (500 mg/m²) to be Administered Every 8 Hours

Body Surface Area* (m ²)	Dose Every 8 Hours (mg)
0.5	300
0.75	400
1	500
1.25	600
1.5	800

*Body surface area can be calculated using the following equation:

$$BSA = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

Since CRIXIVAN[®] must be taken at intervals of 8 hours, a schedule convenient for the patient should be developed. For optimal absorption, indinavir sulfate should be administered without food but with water, 1 hour before or 2 hours after a meal. Alternatively, indinavir sulfate may be administered with other liquids such as skim milk, juice, coffee, or tea, or a light meal (e.g., dry toast with jelly, apple juice, and coffee with skim milk and sugar or corn flakes, skim milk and sugar) (see DETAILED 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.

It is also recommended that children who weigh less than 20 kg drink at least 75 mL/kg/day and that children who weigh 20 to 40 kg drink at least 50 mL/kg/day.

In addition to adequate hydration, medical management of 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.

Concomitant Therapy

Delavirdine

Dose reduction of CRIXIVAN[®] to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day (see WARNINGS AND PRECAUTIONS, Drug Interactions and DETAILED PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Delavirdine).

Efavirenz

Dose increase of CRIXIVAN[®] to 1000 mg every 8 hours is recommended when administering efavirenz concurrently (consult also the complete prescribing information for efavirenz) (see WARNINGS AND PRECAUTIONS, Drug Interactions and DETAILED PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Efavirenz).

Itraconazole

Dose reduction of CRIXIVAN[®] to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently (see WARNINGS AND PRECAUTIONS, Drug Interactions and DETAILED PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Itraconazole).

Ketoconazole

Dose reduction of CRIXIVAN[®] to 600 mg every 8 hours is recommended when administering ketoconazole concurrently (see WARNINGS AND PRECAUTIONS, Drug Interactions and DETAILED PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Ketoconazole).

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 (see WARNINGS AND PRECAUTIONS, Drug Interactions and DETAILED PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Rifabutin).

Other:

Hepatic Insufficiency Due to Cirrhosis

Dose reduction of indinavir sulfate to 600 mg every 8 hours should be considered in patients with mild-to-moderate hepatic insufficiency due to cirrhosis (see DETAILED PHARMACOLOGY, Pharmacokinetics Hepatic Insufficiency Due to Cirrhosis).

Missed Dose

If a dose is missed by more than 2 hours, do not take it later in the day. Simply continue to follow the usual schedule.

OVERDOSAGE

There have been reports of human overdosage with CRIXIVAN[®] (indinavir sulfate). The most commonly reported symptoms were gastrointestinal (e.g., nausea, vomiting, diarrhea) and renal (e.g., nephrolithiasis/urolithiasis, flank pain, hematuria).

It is not known whether indinavir sulfate is dialyzable by peritoneal dialysis or hemodialysis.

Although no data are available, administration of activated charcoal may be used to aid in removal of unabsorbed drug.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CRIXIVAN[®] (indinavir sulfate) is a selective protease inhibitor active against the Human Immunodeficiency Virus (HIV-1).

HIV protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV. Indinavir sulfate 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 Potency

The relationship between *in vitro* susceptibility of HIV to indinavir sulfate and inhibition of HIV replication in humans has not been established. The *in vitro* activity of indinavir sulfate was assessed in cell lines of lymphoblastic and monocytic origin and in peripheral blood

lymphocytes. HIV 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 reverse transcriptase. The IC₉₅ (95% inhibitory concentration) of indinavir sulfate in these test systems was in the range of 25 to 100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational nonnucleoside (L-697,661), indinavir sulfate showed synergistic activity in cell culture.

Virus Mutations

Isolates of HIV with reduced susceptibility to the drug have been recovered from some patients treated with indinavir sulfate. 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, 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. In general, higher levels of resistance were associated with the co-expression of greater numbers of substitutions.

Cross-resistance between indinavir sulfate and HIV reverse transcriptase inhibitors is unlikely because the enzyme targets involved are different. Cross-resistance was noted between indinavir sulfate and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir sulfate and other HIV-protease inhibitors.

Pharmacokinetics

Table 1 Summary of Indinavir’s Pharmacokinetic Parameters in adult and pediatric patients

Regimen	AUC _{0-8hr} (nM•hour)	C _{max} (nM)	C _{8hrs} (nM)	n
Adult patients, 800 mg every 8 hrs	30,691 ± 11,407	12,617 ± 4037	251 ± 178	16
Pediatric patients, 500 mg/m ² every 8 hours	38,742 ± 24,098	17,181 ± 9,808	199 ± 358	34 for AUC and C _{max} ; 29 for C _{8hrs}

Absorption: Pharmacokinetic parameters of indinavir are summarized in Table 1. In adult patients, 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. Between 800 mg and 1000 mg dose levels, the deviation from dose-proportionality is less pronounced.

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 (see DOSAGE AND ADMINISTRATION).

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 sulfate, $83 \pm 1\%$ (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 P450 (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 and Conditions

Pediatrics: The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to those previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours (see Table 1). The $\text{AUC}_{0-8\text{hr}}$ and C_{\max} values were comparable or slightly higher to those previously observed in HIV-infected adults receiving the recommended dose; the trough concentrations ($C_{8\text{h}}$) were substantially lower in children with many children having values below 100 nM.

Gender: The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received indinavir 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). The mean percentage decrease in $\text{AUC}_{0-8\text{h}}$, C_{\max} and $C_{8\text{h}}$ for females relative to males was 13%, 13%, and 22%, respectively. 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).

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 Due to Cirrhosis).

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

For information on pharmacokinetic drug-drug interactions, see DRUG INTERACTIONS - Overview and DETAILED PHARMACOLOGY – Drug Interactions.

Pregnant Women

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 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)

Absorption of orally administered indinavir sulfate is rapid. Peak plasma concentration occurs within 1 hour and is not dose dependent. The oral absorption of a 400 mg dose of indinavir sulfate is reduced by 78% when administered with a standard meal high in calories, fat and protein contents. Indinavir sulfate has a relatively short half-life of 1.8 hours. There is very little drug accumulation following either an 8 hour or 6 hour dosing regimen over the clinical dose range.

Indinavir is widely distributed in the body and is approximately 60% bound to human plasma proteins. Less than 20% of indinavir is excreted unchanged in the urine. Following a single 400 mg dose of indinavir sulfate, patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had a mean AUC which was found to be higher by approximately 60% compared to that in healthy subjects and the half-life increased to approximately 2.8 hours, a reflection of reduced metabolism.

Therapy with indinavir sulfate should be initiated at the full recommended dose to increase suppression of viral replication and therefore inhibit the emergence of resistant virus (see DOSAGE AND ADMINISTRATION). No titration is necessary upon initiating therapy.

STORAGE AND STABILITY

Store in a tightly closed container at room temperature (15°C-30°C). Protect from moisture. CRIXIVAN[®] capsules are sensitive to moisture. CRIXIVAN[®] should be dispensed and stored in the original container. The desiccant should remain in the original bottle.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Capsules of indinavir sulfate are formulated as a sulfate salt ethanolate and are available for oral administration in strengths of 100 mg, 200 mg, 300 mg, or 400 mg of the active ingredient, indinavir. Each capsule also contains the following non-medicinal ingredients: anhydrous lactose (as a diluent) and magnesium stearate (as a lubricant), and gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide (empty capsule shell).

Dosage forms and packaging

CRIXIVAN[®] 100 mg, are semi-translucent, white capsules, coded CRIXIVAN[™] 100 mg in green. Available in bottles of 180 capsules, with desiccant.

CRIXIVAN[®] 200 mg, are white semi-translucent capsules, coded CRIXIVAN[™] 200 mg in blue. Available in bottles of 180 , 270 and 360 capsules, with desiccant.

CRIXIVAN[®] 300 mg, are white opaque capsules, coded CRIXIVAN[™] 300 mg in red. Available in bottles of 120 and 240 capsules, with desiccant.

CRIXIVAN[®] 400 mg, are white semi-translucent capsules, coded CRIXIVAN[™] 400 mg in green. Available in bottles of 18, 90, 120 and 180 capsules, with desiccant and in blisters of 42 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

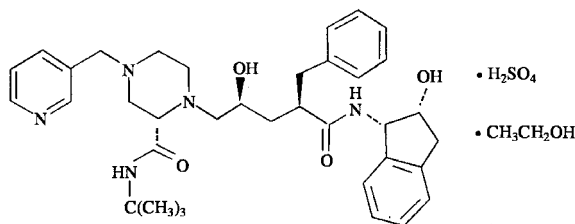
Proper name: indinavir sulfate (as the ethanolate salt)

Chemical name: [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.

Molecular formula: $C_{36}H_{47}N_5O_4 \cdot H_2SO_4 \cdot CH_3CH_2OH$

Molecular mass : 757.94

Structural formula:



Physicochemical properties:

Description: Indinavir sulfate ethanolate is a white to off-white, free-flowing crystalline powder.

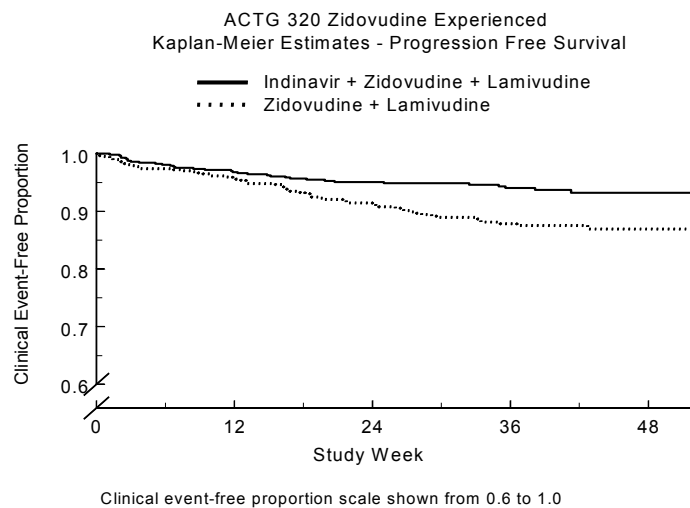
CLINICAL TRIALS

Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of indinavir sulfate 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. According to the protocol, 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, mean baseline CD4 count 87 cells/mm³, median time of prior zidovudine therapy 21 months). The median length of follow-up was 38 weeks with a maximum of 52 weeks.

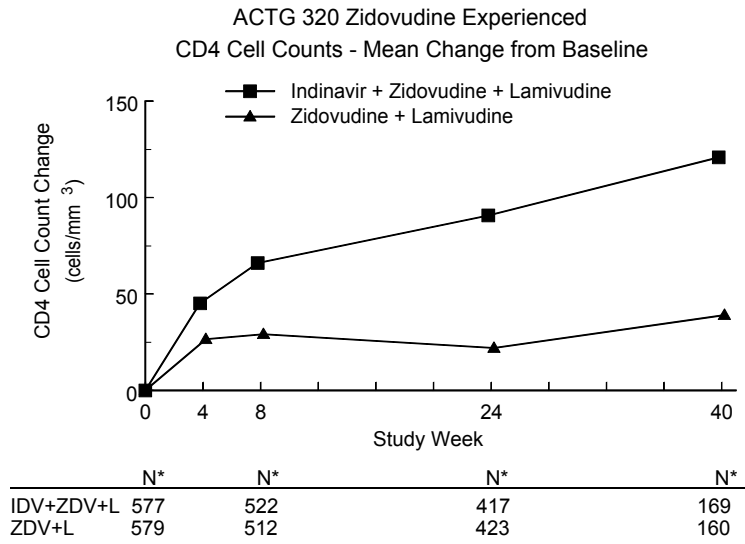
A total of 33 (6%, n=577) patients progressed to an ADI or death in the group treated with the combination containing indinavir sulfate compared to 63 (11%, n=579) patients in the group treated with the nucleoside analogue combination. This represents a 50% reduction in the risk of progression to an ADI or death in the group treated with the combination containing indinavir sulfate relative to the group treated with the nucleoside analogue combination (p=0.001). The estimates for the proportion of patients surviving without an ADI are summarized in Figure 1. A total of 10 deaths (1.7%, n=577) occurred in the group treated with the combination containing indinavir sulfate and 19 deaths (3.3%, n=579) occurred in the group treated with the nucleoside analogue combination. Although there was a 49% reduction in the risk of overall mortality associated with indinavir sulfate, the difference was not statistically significant.

Mean changes in CD4 cell count are summarized in Figure 2.

Study ACTG 320: Figure 1

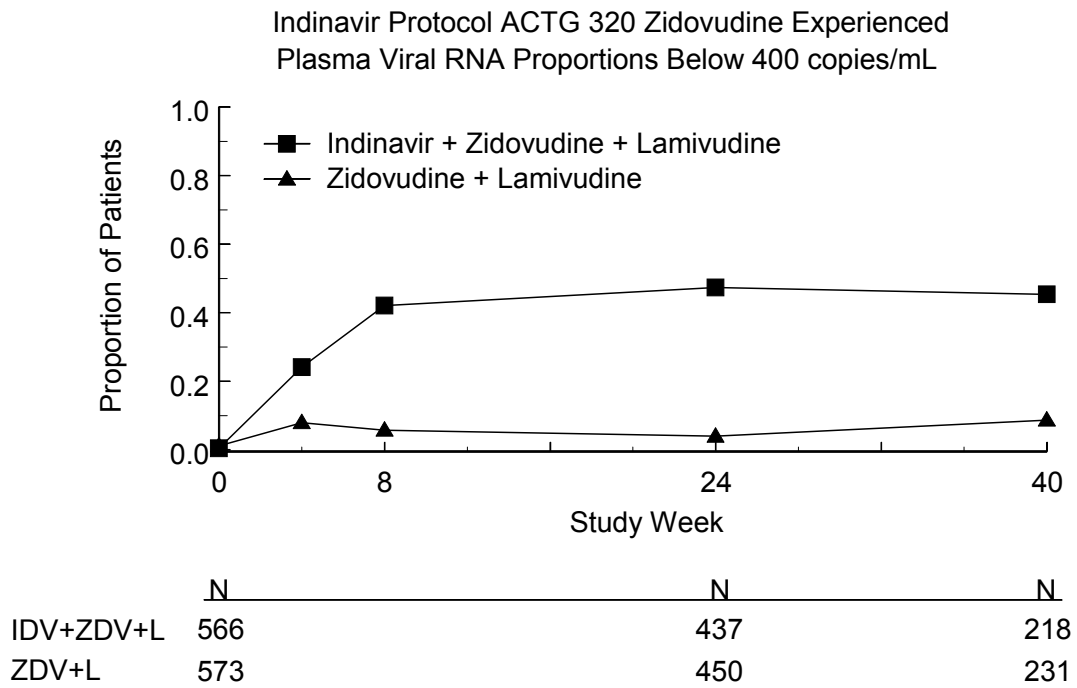


Study ACTG 320: Figure 2



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

Study ACTG 320: Figure 3

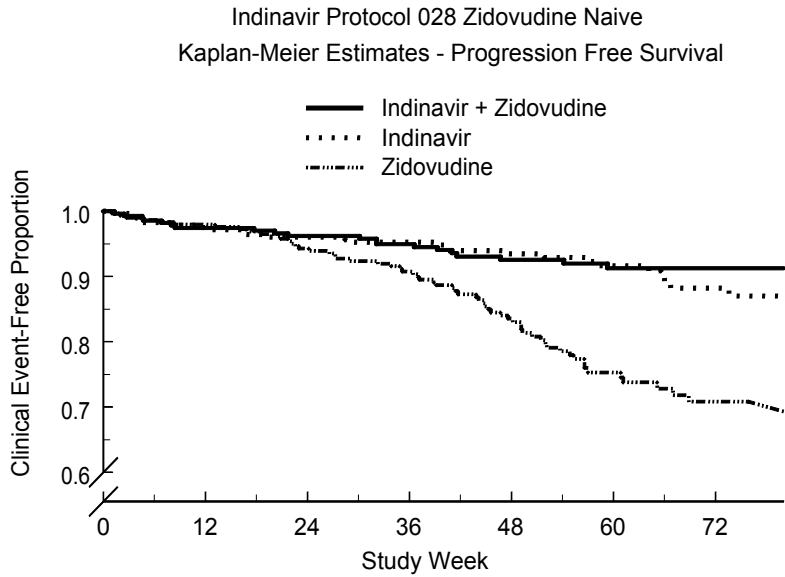


Study 028, a double-blind, multicenter, randomized, clinical endpoint trial compared the effects of indinavir sulfate plus zidovudine with those of indinavir sulfate alone or zidovudine alone on the progression to an ADI or death, and on surrogate marker responses. According to the protocol, all patients 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 (at median time study week 40). The median length of follow-up was 56 weeks with a maximum of 97 weeks.

A total of 20 (6%, n=332) patients progressed to an ADI or death in the group treated with indinavir sulfate plus zidovudine compared to 61 (18%, n=332) patients in the group treated with zidovudine alone. This represents a 70% reduction in the risk of progression to an ADI or death in the group initially treated with indinavir sulfate plus zidovudine compared to the group initially treated with zidovudine alone (p<0.0001). A total of 26 (8%, n=332) patients progressed to an ADI or death in the group treated with indinavir sulfate alone. This represents a 61% reduction in the risk of progression to an ADI or death in the group treated with indinavir sulfate alone compared to the group treated with zidovudine alone (p<0.0001). The estimates for the proportion of patients surviving without an ADI are summarized in Figure 4. A total of 8 (2.4%, n=332) deaths occurred in the group treated with indinavir sulfate plus zidovudine, 5 (1.5%, n=332) in the group treated with indinavir sulfate alone, and 11 (3.3%, n=332) in the group treated with zidovudine alone. No statistically significant differences in the risk of death among treatment groups was demonstrated.

Mean changes in CD4 cell counts are summarized in Figure 5. The proportions of patients with serum viral RNA below 500 copies/mL, the limit of quantification of the assay, are summarized in Figure 6.

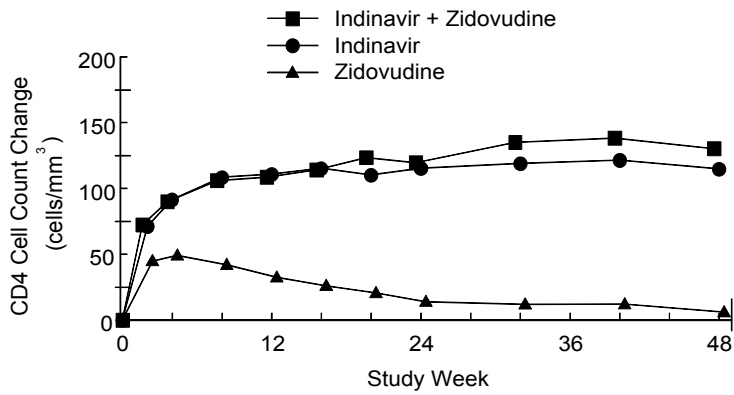
Study 028: Figure 4



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

Study 028: Figure 5

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

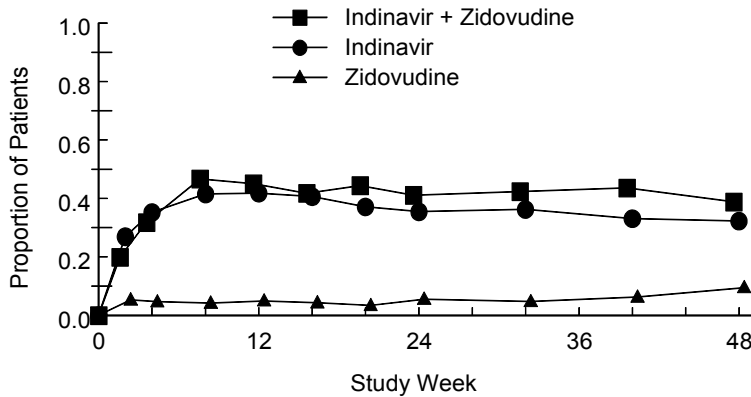


	N*	N*	N*
IDV+ZDV	332	277	214
IDV	332	298	222
ZDV	332	295	213

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

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

Study 028: Figure 6
 Indinavir Protocol 028 Zidovudine Naïve
 Serum Viral RNA - Proportions Below 500 Copies/mL



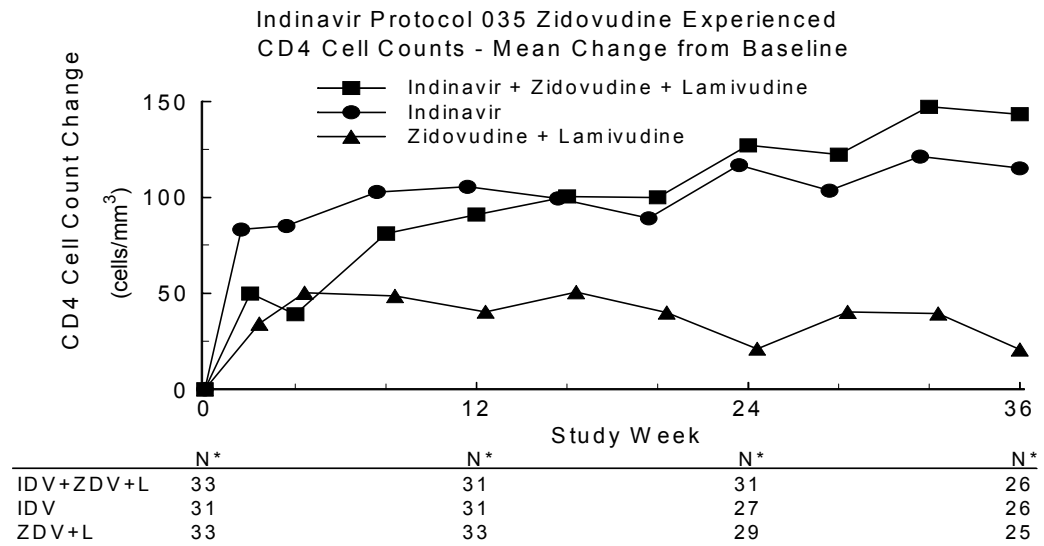
	N*	N*	N*
IDV+ZDV	328	267	198
IDV	329	293	204
ZDV	328	288	200

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

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

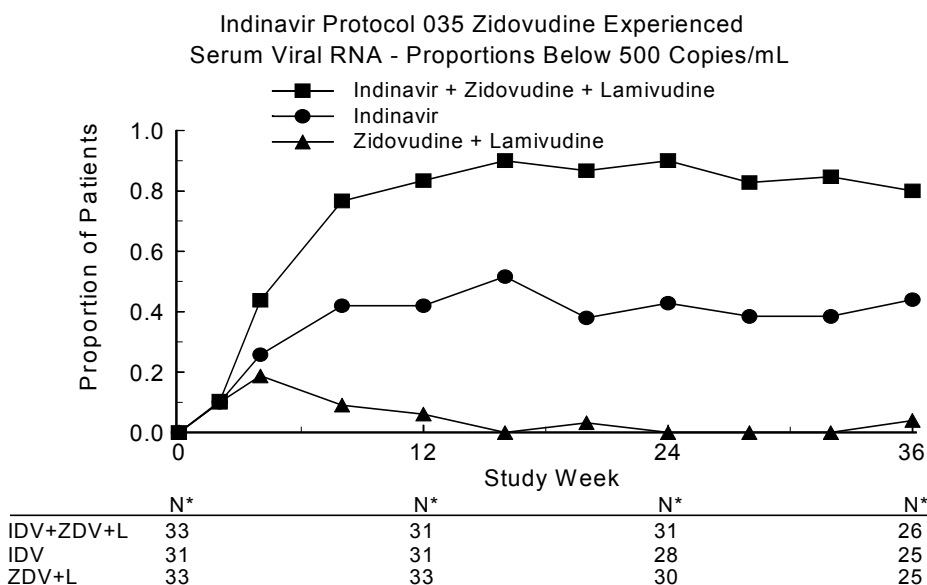
Study 035 was a multicenter, randomized, surrogate marker trial comparing the effects of indinavir sulfate with those of indinavir sulfate plus zidovudine plus lamivudine and those of zidovudine plus lamivudine on CD4 cell counts and serum viral RNA. According to the protocol, all patients were protease-inhibitor and lamivudine naïve, and zidovudine experienced, with CD4 cell counts between 50 and 400 cells/mm³ and serum viral RNA levels 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 indinavir sulfate plus zidovudine plus lamivudine after at least 24 weeks of double-blind, randomized therapy and is ongoing. 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/mm³, and the mean baseline serum viral RNA was 4.62 log₁₀ copies/mL (41,230 copies/mL). Mean changes in CD4 cell counts during the double-blind portion are summarized in Figure 7. 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 summarized in Figure 8.

Study 035: Figure 7



*N = Number during double-blind portion with CD4 cell count measurement at Weeks 0, 12, 24, 36
 Treatment was changed to open-label therapy with indinavir sulfate plus zidovudine plus lamivudine after at least 24 weeks of double-blind therapy (median length of double-blind follow-up: 41 weeks).
 N decreases after Week 24 due to variable lengths of double-blind follow-up.

Study 035: Figure 8



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

Treatment was changed to open-label therapy with indinavir sulfate plus zidovudine plus lamivudine after at least 24 weeks of double-blind therapy (median length of double-blind follow-up: 41 weeks). N decreases after Week 24 due to variable lengths of double-blind follow-up.

DETAILED PHARMACOLOGY

Pharmacokinetics

Absorption in Adult Patients

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).

Absorption in Pediatric Patients

In HIV-infected pediatric patients, a dosage regimen of indinavir sulfate capsules, 500 mg/m² every 8 hours, produced AUC_{0-8hr} of $38,742 \pm 24,098$ nM•hour (n=34), C_{max} of $17,181 \pm 9,808$ nM (n=34), and trough concentration of 199 ± 358 nM (n=29).

The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to those previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC_{0-8hr} and C_{max} values were comparable or slightly higher to those previously observed in HIV-infected adults receiving the recommended dose; the trough concentrations (C_{0-8h}) were substantially lower in children with many children having values below 100 nM.

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 (see DOSAGE AND ADMINISTRATION).

Distribution

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

In dogs, the ratio of mean fetal plasma to mean maternal plasma indinavir concentrations was 0.49 both 1 and 2 hours after dosing. Distribution of indinavir across the placental barrier was limited and the ratio of AUC in the fetus to that in maternal plasma averaged 0.02 and 0.2 in rabbits and rats, respectively.

Metabolism

Following a 400 mg dose of ¹⁴C-indinavir sulfate, 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 P450 (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.

Hepatic Insufficiency Due to Cirrhosis

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 Due to Cirrhosis).

Renal Insufficiency

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

Drug Interactions

Delavirdine

Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400 mg single dose of indinavir sulfate with delavirdine (400 mg three times a day) resulted in indinavir AUC values slightly less than those observed following administration of an 800 mg dose of indinavir sulfate alone. Also, coadministration of a 600 mg dose of indinavir sulfate with delavirdine (400 mg three times a day) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800 mg dose of indinavir sulfate alone. Indinavir had no effect on delavirdine pharmacokinetics (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Delavirdine).

Efavirenz

When indinavir sulfate (800 mg every 8 hours) was given with efavirenz (200 mg once daily) for two weeks, the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Efavirenz).

Itraconazole

In a multiple-dose study, administration in the fasted state of itraconazole capsules 200 mg twice daily with indinavir sulfate 600 mg every 8 hours resulted in an indinavir AUC similar to that observed during administration of indinavir sulfate 800 mg every 8 hours alone for one week (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Itraconazole).

Ketoconazole

In a single-dose study, administration of a 400-mg dose of ketoconazole with a 400-mg dose of indinavir sulfate resulted in a $68\% \pm 48\%$ increase in indinavir AUC compared to a 400-mg dose of indinavir sulfate alone. In a multiple-dose study, administration of ketoconazole 400 mg once daily with indinavir sulfate 600 mg every 8 hours resulted in an $18\% \pm 17\%$ decrease in indinavir AUC compared to 800 mg every 8 hours alone (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Ketoconazole).

Rifabutin

The coadministration of indinavir sulfate (800 mg every 8 hours) with rifabutin either 300 mg once daily or 150 mg once daily was evaluated in two separate clinical studies. The results of these studies showed a decrease in indinavir AUC ($32\% \pm 19\%$ and $31\% \pm 15\%$, respectively) vs indinavir 800 mg every 8 hours alone, and an increase in rifabutin AUC ($204\% \pm 142\%$ and $60\% \pm 47\%$, respectively) vs rifabutin 300 mg once daily alone). This increase in rifabutin plasma concentrations is likely related to inhibition of CYP3A4-mediated metabolism of rifabutin by indinavir. A dosage reduction of rifabutin and a dosage increase of indinavir sulfate are necessary when rifabutin is coadministered with indinavir sulfate (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Rifabutin).

Rifampin

Administration of indinavir sulfate (800 mg every 8 hours) with rifampin (600 mg once daily) for one week resulted in an $89\% \pm 9\%$ decrease in indinavir AUC. Rifampin is a potent inducer of P450 (CYP3A4) which markedly diminishes plasma concentrations of indinavir. Therefore, CRIVAN[®] and rifampin should not be coadministered (see WARNINGS AND PRECAUTIONS, Drug Interactions, Rifampin).

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

In a published study, eight HIV-negative volunteers received indinavir 800 mg every eight hours for four doses prior to and at the end of a 14-day course of St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg three times daily. Indinavir plasma pharmacokinetics were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC_{0-8h} of indinavir was decreased $57\% \pm 19\%$ and the C_{8h} of indinavir was decreased $81\% \pm 16\%$ compared to when indinavir was taken alone. All subjects demonstrated a decrease in AUC_{0-8h} (range 36 to 79%) and a decrease in C_{8h} (range 49 to 99%). (See WARNINGS AND PRECAUTIONS, Drug Interactions, St. John's wort.)

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 AND PRECAUTIONS, Drug Interactions, Sildenafil).

MICROBIOLOGY

VIROLOGY

Indinavir at concentrations of 50 to 100 nM mediated 95% inhibition (IC₉₅) 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 of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including 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, however, CD4 cell counts were often sustained above pretreatment levels. When loss of viral RNA suppression occurred, it was typically associated with replacement of circulating susceptible virus with resistant viral 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. No single substitution was capable of engendering measurable 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.

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

Genotypic Resistance in Clinical Studies

Study 006 was a dose-ranging study in which patients were initially treated with indinavir sulfate at a dose of <2.4 g/day followed by 2.4 g/day. Study 019 was a randomized comparison of indinavir sulfate (IDV) 600 mg every 6 hours, indinavir sulfate plus zidovudine (ZDV), and zidovudine alone. Table 3 shows the incidence of genotypic resistance at 24 weeks in these studies.

Treatment Group	Resistance to IDV n/N'	Resistance to ZDV n/N'
IDV	-	-
<2.4g/day	31/37 (84%)	-
2.4g/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.

Cross Resistance

HIV-1 patient isolates with reduced susceptibility to indinavir sulfate 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 sulfate 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 sulfate. The concomitant use of indinavir sulfate 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.

TOXICOLOGY

Acute Toxicity

The approximate oral LD₅₀ for indinavir is >5000 mg/kg in rats and mice. The approximate intraperitoneal LD₅₀ is 5000 mg/kg in mice and >5000 mg/kg in rats.

Long-Term Toxicity

Crystals (consistent with parent drug) have been seen in the urine of rats treated with indinavir at doses 50 mg/kg/day. In monkeys treated with indinavir at doses up to 40 mg/kg twice a day, crystalluria was not observed; however, it was observed in one monkey at 160 mg/kg twice a day. In dogs treated with indinavir at doses up to 40 mg/kg/day, crystalluria was not observed; however, it was observed in one dog at 80 mg/kg/day. The crystals have not been associated with drug-induced renal injury including no increases in serum urea nitrogen or creatinine in any of these species. Renal histologic changes have not been seen in rats at doses up to 640 mg/kg/day for up to 53 weeks, in dogs at doses up to 80 mg/kg/day for up to 53 weeks, and in monkeys at doses up to 160 mg/kg twice a day for up to 5 weeks. An increase in thyroidal weight and thyroidal follicular cell hyperplasia, due to an increase in thyroxine clearance, was seen in rats treated with indinavir at doses 160 mg/kg/day. An increase in hepatic weight occurred in rats treated with indinavir at doses 40 mg/kg/day and was accompanied by hepatocellular hypertrophy at doses 320 mg/kg/day; this change was seen without histologic evidence of hepatic injury at doses up to 640 mg/kg/day in this species.

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest doses in the mouse study were 480 mg/kg/day (males) and 640 mg/kg/day (females), which produced daily systemic exposures approximately 1.7 and 2.6 times higher, respectively, than the daily systemic exposure in humans at the recommended daily dose. In rats, an increased incidence of thyroid adenomas was seen at the highest dose tested, 640 mg/kg/day (males and females). At that dose, daily systemic exposure in rats was approximately 1.3 to 2.3 times higher than daily systemic exposure in people.

Mutagenicity

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 *in vitro* mammalian cell mutagenesis assays.

Reproduction and Teratology

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. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

Developmental toxicity studies performed in rats, rabbits, and dogs (at doses which produced systemic exposures comparable to or slightly greater than human exposure) revealed no evidence of teratogenicity. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs at doses \geq 160 mg/kg/day and of cervical ribs at 640 mg/kg/day were seen in rats. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. Estimates of placental transfer based on the ratio of fetal to maternal plasma concentrations at or near the T_{\max} indicated a significant *in utero* exposure in rats (range 5-33%; n=4 animals) and in dogs (range 46-58%; n=4 animals). The absence or low levels of indinavir in rabbit fetal plasma did not permit estimation of placental transfer in this species.

Studies in which rats were administered 40 or 640 mg/kg/day demonstrated that indinavir is excreted in milk of lactating rats. The ratios of indinavir in milk to that in plasma were greater than 1.

In Rhesus monkeys, administration of indinavir sulfate to neonates caused a mild exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth. Administration of indinavir sulfate to pregnant Rhesus monkeys during the third trimester did not cause a similar exacerbation in neonates; however, only limited placental transfer of indinavir sulfate occurred.

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PART III: CONSUMER INFORMATION**PrCRIXIVAN[®]
indinavir sulfate**

This leaflet is part III of a three-part "Product Monograph" published when CRIXIVAN[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CRIXIVAN[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Your physician has prescribed CRIXIVAN[®] for you because you have HIV infection. CRIXIVAN[®] can help reduce your chances of getting illnesses associated with HIV infection. CRIXIVAN[®] can also help lower the amount of HIV in your blood (called "viral load") and raise your CD4 (T) cell count. CRIXIVAN[®] may not have these effects in all patients.

HIV is a blood-borne disease spread by contact with blood or sexual contact with an infected individual.

What it does:

CRIXIVAN[®] is a member of a class of drugs called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the amount of virus within the body.

When it should not be used:

- Do not take CRIXIVAN[®] if you experience a severe allergic reaction to any component of the drug (see What the important nonmedicinal ingredients are).
- Do not take CRIXIVAN[®] with amiodarone, ergot derivatives, cisapride (no longer marketed in Canada), pimozide, midazolam and triazolam.

What the medicinal ingredient is:

Indinavir sulfate

What the important nonmedicinal ingredients are: Each capsule contains the following non-medicinal ingredients: anhydrous lactose (as a dry binder/filler) and magnesium stearate (as a lubricant); and gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide (empty capsule shell).

What dosage forms it comes in:

CRIXIVAN[®] is available as white semi-translucent capsules containing either 100, 200, 300 or 400 mg of indinavir as the active ingredient.

WARNINGS AND PRECAUTIONS**BEFORE you use CRIXIVAN[®] talk to your doctor if:**

- You have past or present medical problems, including liver or kidney problems, diabetes, hemophilia, high cholesterol and if you are taking cholesterol-lowering medicines called "statins".
- You are taking or plan to take any medication, such as non-prescription drugs or natural health products including herbs or dietary supplements. Some medicines should not be taken with CRIXIVAN[®] or may require a dosage adjustment (see Interactions with this medication).
- You are pregnant or planning to become pregnant. It is not known whether taking CRIXIVAN[®] may be harmful to an unborn baby. If you are pregnant, you should take CRIXIVAN[®] only if your doctor decides it is needed.
- You are breastfeeding or planning to do so. You should not breastfeed while taking CRIXIVAN[®]. Consult your doctor.

Other Warnings

- CRIXIVAN[®] is not a cure for HIV infection and you may continue to develop infections or other illnesses associated with HIV disease. Continue to see your doctor regularly and report any medical problems you have.
- CRIXIVAN[®] does not prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex and take precautions to prevent others from coming into contact with your blood and other body fluids.
- The long term effects of CRIXIVAN[®] are unknown. Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Use in children.

CRIXIVAN[®] can be taken by children 3 years of age and older who are able to swallow capsules.

INTERACTIONS WITH THIS MEDICATION

Medications that may **not** be taken with CRIXIVAN[®] because it could result in serious or life-threatening events (such as problems with heart rhythm or excessive sleepiness) are

amiodarone (e.g. Cordarone[®]), alprazolam (e.g. Xanax[®]), triazolam (e.g. Halcion[®]), astemizole* (e.g. Hismanal[™]), cisapride* (e.g. Propulsid[®]), terfenadine* (e.g. Seldane[®]), midazolam (e.g. Versed[®]), pimozide (e.g. Orap[®]), rifampin (e.g. Rifadin[®], Rifater[®], Rimactane[®]) and ergot medications (e.g. Cafergot[®], Ergomar[®], Wigraine[®]). Consult your physician before taking CRIXIVAN[®] with any other medication.

If you are taking protease inhibitors including CRIXIVAN[®], you should not be taking some of the cholesterol-lowering medicines called “statins” (e.g. lovastatin and simvastatin) as severe muscle pain and weakness have occurred when these drugs are taken together. Consult your physician if you have further questions.

Taking CRIXIVAN[®] with St. John’s wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John’s wort is not recommended as it may decrease the effect of CRIXIVAN[®] or other HIV-related drugs.

CRIXIVAN[®] may be taken with a number of medications that are commonly used by people with HIV infection. These include zidovudine (AZT[™], e.g. Retrovir[®]), didanosine (ddI, e.g. Videx[®]), lamivudine (e.g. 3TC[®]), stavudine (d4T, e.g. Zerit[™]), fluconazole (e.g. Diflucan[®]), isoniazid, clarithromycin (e.g. Biaxin[®]), trimethoprim/sulfamethoxazole (e.g. Bactrim[®], Roubac[®], Septra[®]), and methadone.

Other medications may be taken with CRIXIVAN[®] but require dosage adjustment of that medication or of CRIXIVAN[®]. These include rifabutin (e.g. Mycobutin[®]), ketoconazole (e.g. Nizoral[®]), itraconazole (e.g. Sporanox[®]), delavirdine (e.g. Rescriptor[®]), and efavirenz (e.g. Sustiva[®]).

Tell your doctor if you are taking calcium channel blockers (drugs to treat hypertension or chest pain).

Tell your doctor if you are taking venlafaxine (e.g. Effexor[®]).

Tell your doctor if you are taking trazodone (e.g. Desyrel[®]).

Tell your doctor if you are taking sildenafil (e.g. Viagra[®]).

Can I drive or operate machinery while using CRIXIVAN[®]?

Dizziness and blurred vision have been reported during treatment with CRIXIVAN[®]. If you experience these you should avoid driving or operating machinery.

PROPER USE OF THIS MEDICATION

Usual dose:

CRIXIVAN[®] is in capsule form and must be taken orally. Take 800 mg (usually given as two 400 mg capsules) at regular 8-hour

intervals. CRIXIVAN[®] must be taken at intervals of 8 hours for full effectiveness.

The dose for children and adolescents will be determined by the physician.

It is very important to take CRIXIVAN[®] exactly as prescribed to help ensure full effectiveness of the product. Do not stop taking it without first telling your doctor.

CRIXIVAN[®] should be taken with water 1 hour before or 2 hours after a meal. If water is not preferred, CRIXIVAN[®] can be taken with skimmed or fat-free milk, juice, coffee, or tea; or a light meal such as dry toast and jam or fruit conserve, juice and coffee with skimmed or fat-free milk and sugar; or corn flakes, skimmed or fat-free milk and sugar. At any other time you can follow your regular diet.

Taking CRIXIVAN[®] with a meal that is high in calories, fat, and protein reduces your body's ability to absorb the drug and in turn reduces its effectiveness.

It is important for adults to drink at least 1.5 liters (approximately 48 ounces) of liquids during each day to ensure adequate hydration. It is also important for children and adolescents to drink enough liquids during the course of the day. The physician will tell you the amount of liquid your child should drink. This may help reduce the incidence of kidney stones (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

If you take didanosine with CRIXIVAN[®], take them at least one hour apart on an empty stomach.

Missed Dose:

Take CRIXIVAN[®] 3 times a day at regular 8-hour intervals. However, if you miss a dose by more than 2 hours, do not take it later in the day. Simply continue to follow your usual schedule. Do not take a double dose of CRIXIVAN[®].

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects. CRIXIVAN[®] has been shown to be generally well tolerated. There have been reports of kidney stones and in some of these patients this led to more severe kidney problems including kidney failure. In most cases, kidney impairment and kidney failure were temporary and reversible. Call your physician if you develop sudden severe back pain, with or without blood in the urine caused by kidney stones.

* no longer marketed in Canada

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

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

Other side effects include weakness/fatigue; low red blood cell count; heart problems including heart attack; abdominal pain/swelling; inflammation of the pancreas; inflammation of the kidneys; infection of the kidneys; decreased kidney function; diarrhea; upset stomach; nausea; dizziness; headache; dry skin; change in skin color; hair loss; ingrown toenails with or without infection; crystals in the urine; numbness of the mouth; rash; severe skin reactions; allergic reactions; and taste perversion.

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

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

There have been reports of diabetes and increased blood sugar (also called hyperglycemia) in patients treated with protease inhibitors. In some of these patients, this led to ketoacidosis, a serious condition resulting from poorly controlled blood sugar. Before starting protease inhibitors, some patients already had diabetes, others did not. Some patients required adjustments to their diabetes medication. Other patients needed new diabetes medication.

Your physician has a more complete list of side effects.

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

In addition, tell your physician if you experience any symptoms that suggest an allergic reaction after taking CRIXIVAN[®].

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Kidney problems including kidney stones, kidney failure and symptoms such as back pain, blood in the urine		✓	
	Hemolytic anemia, the rapid breakdown of blood cells and symptoms such as jaundice and dark urine		✓	
Uncommon	Severe allergic reaction/difficulty of breathing		✓	✓
	Increased bleeding in hemophiliacs		✓	
	New onset/worsening of diabetes		✓	
Uncommon	Hepatitis		✓	

This is not a complete list of side effects. For any unexpected effects while taking CRIXIVAN[®], contact your doctor or pharmacist.

Other considerations

Although CRIXIVAN[®] is not a cure for HIV infection, CRIXIVAN[®] can help increase the amount of time you will spend living without disease associated with HIV.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of

inflammation from previous infections may occur when combination antiretroviral treatment is started.

See your physician for more details.

<http://www.merckfrosst.com>
or by contacting the sponsor, Merck Frosst Canada Ltd.,
at: 1-800-567-2594,

This leaflet was prepared by Merck Frosst Canada Ltd.

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HOW TO STORE IT

Protect from moisture.

- Keep CRIXIVAN[®] capsules in the bottle they came in and at room temperature (15°C-30°C).
- Keep CRIXIVAN[®] capsules dry by leaving the small desiccant in the bottle. Keep the bottle closed.

Keep all medicines out of the reach of children.

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REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this vaccine you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

or Merck Frosst Canada Ltd. by:

Toll-free telephone: 800-567-2594
Toll-free fax: 877-428-8675
By regular mail:
Merck Frosst Canada Ltd.
P.O. Box 1005
Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Before contacting Health Canada or Merck Frosst, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: