



Dear Doctor:

We are pleased to enclose the article “Managing the Treatment-Experienced Patient” by Eric S. Daar, as published as the third monograph in the Clinical Guide series *New Treatment Goals for Adult HIV Infection*, a special publication of the *Journal of Clinical Outcomes Management*, which was funded by Merck & Co., Inc.

About ISENTRESS® (raltegravir) Tablets

ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in 2 controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral—nonnucleoside reverse transcriptase inhibitor (NNRTI), nucleoside reverse transcriptase inhibitor (NRTI), and protease inhibitor (PI)—treatment-experienced adults. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response. The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients. There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection.

Important Safety Information for ISENTRESS

During the initial phase of treatment, immune reconstitution syndrome can occur, which may necessitate further evaluation and treatment.

Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (eg, rifampin) because of reduced plasma concentrations of ISENTRESS.

The drug-related adverse reactions ($\geq 2\%$) of moderate to severe intensity reported in subjects in either the ISENTRESS or placebo treatment group were diarrhea, nausea, and headache. The most common adverse reactions ($>10\%$) of all intensities reported in either treatment group, regardless of causality, were diarrhea, nausea, headache, and pyrexia.

Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use ISENTRESS with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

About CRIXIVAN® (indinavir sulfate) Capsules

CRIXIVAN in combination with other antiretroviral agents is indicated for the treatment of HIV infection. This indication is based on 2 clinical trials of approximately 1 year’s duration that demonstrated (1) a reduction in the risk of AIDS-defining illness or death and (2) a prolonged suppression of HIV RNA.

Important Safety Information for CRIXIVAN® (indinavir sulfate)

Contraindications

CRIXIVAN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Drug Interactions With CRIXIVAN: Contraindicated Drugs

Drug Class	Drugs Within Class That are Contraindicated With CRIXIVAN	Potential Serious and/or Life-Threatening Reactions due to Inhibition of CYP3A4 by CRIXIVAN Resulting in Elevated Plasma Concentrations of These Drugs
Antiarrhythmics	Amiodarone	Cardiac arrhythmias
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues
Sedative/hypnotics	Alprazolam, oral midazolam, triazolam	Prolonged or increased sedation or respiratory depression
GI motility agents	Cisapride	Cardiac arrhythmias
Neuroleptics	Pimozide	Cardiac arrhythmias

Selected Warnings

ALERT: Find out about medicines that should NOT be taken with CRIXIVAN.

Nephrolithiasis/uroolithiasis has occurred in clinical studies in adult patients (12.4%; range across individual trials, 4.7%–34.4%) and in pediatric patients (29%) receiving CRIXIVAN. The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN; however, the risk over time remains relatively constant. In some cases, nephrolithiasis/uroolithiasis has been associated with renal insufficiency or acute renal failure and pyelonephritis with or without bacteremia. If signs or symptoms of nephrolithiasis/uroolithiasis occur (including flank pain with or without hematuria or microscopic hematuria), temporary interruption (eg, 1–3 days) or discontinuation of therapy may be considered. Adequate hydration (at least 48 ounces daily for adults) is recommended in all patients treated with CRIXIVAN.

In patients treated with CRIXIVAN, acute hemolytic anemia, including death in some patients, and hepatitis, including hepatic failure and death, have been reported.

There have also been reports of hyperglycemia and new onset or exacerbation of preexisting diabetes mellitus in patients receiving protease inhibitors.

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 metabolized by the CYP3A4 pathway (eg, atorvastatin).

Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving indinavir. Coadministration of CRIXIVAN with these medications is expected to substantially increase plasma concentrations of sildenafil, tadalafil, and vardenafil and may result in an increase in adverse reactions, including hypotension, visual changes, and priapism, which have been associated with sildenafil, tadalafil, and vardenafil.

Additional Drugs That Should NOT be Coadministered With CRIXIVAN® (indinavir sulfate)

Drug Class	Drug Name	Clinical Comment
Herbal products	St. John's wort (<i>Hypericum perforatum</i>) and products containing St. John's wort	<i>Warning:</i> Shown to substantially decrease concentrations of CRIXIVAN and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.
Antimycobacterial	Rifampin	<i>Precaution:</i> May lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors or other coadministered antiretroviral agents.
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	<i>Warning:</i> Not recommended. Potential for serious reactions, such as risk of myopathy including rhabdomyolysis, may be increased.
Protease inhibitor	Atazanavir	<i>Precaution:</i> 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.

Selected Precautions

Indirect hyperbilirubinemia has occurred frequently (in approximately 14% of patients treated with CRIXIVAN in clinical studies) and has infrequently been associated with increases in serum transaminases.

Reports of tubulointerstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leukocyturia (>100 cells/high-power field).

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors.

In patients with hepatic insufficiency due to cirrhosis, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN. Patients with renal insufficiency have not been studied.

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

Indinavir is an inhibitor of the cytochrome P-450 isoform CYP3A4. Coadministration of CRIXIVAN and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects.

Indinavir is metabolized by CYP3A4. Drugs that induce CYP3A4 activity would be expected to increase the clearance of indinavir, resulting in lowered plasma concentrations of indinavir. Coadministration of CRIXIVAN and other drugs that inhibit CYP3A4 may decrease the clearance of indinavir and may result in increased plasma concentrations of indinavir.

Use of CRIXIVAN is not recommended in pregnant patients.

Established and Other Potentially Significant Drug Interactions

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

HIV Antiviral Agents

Drug Name	Effect on Concentration	Clinical Comment
Delavirdine	↑ indinavir	Dose reductions of CRIXIVAN® (indinavir sulfate) to 600 mg q8h should be considered when taking delavirdine 400 mg tid.
Didanosine	n/a	Indinavir and didanosine formulations containing buffer should be administered at least 1 hour apart on an empty stomach.
Efavirenz	↓ indinavir	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg q8h does not compensate for the increased indinavir metabolism due to efavirenz.
Nelfinavir	↑ indinavir	The appropriate doses for this combination with respect to efficacy and safety have not been established.
Nevirapine	↓ indinavir	The appropriate doses for this combination with respect to efficacy and safety have not been established.
Ritonavir	↑ indinavir, ↑ ritonavir	The appropriate doses for this combination with respect to efficacy and safety have not been established. Preliminary clinical data suggest that the incidence of nephrolithiasis is higher in patients receiving indinavir in combination with ritonavir than in those receiving CRIXIVAN 800 mg q8h.
Saquinavir	↑ saquinavir	The appropriate doses for this combination with respect to efficacy and safety have not been established.

Other Agents

Drug Name	Effect on Concentration	Clinical Comment
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with CRIXIVAN.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ indinavir	Use with caution. CRIXIVAN may not be effective because of decreased indinavir concentrations in patients taking these agents concomitantly.
Calcium channel blockers, dihydropyridine: eg, felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted, and clinical monitoring of patients is recommended.

Clarithromycin	↑ clarithromycin, ↑ indinavir	The appropriate doses for this combination with respect to efficacy and safety have not been established.
Inhaled/nasal steroid: fluticasone	↑ fluticasone	Concomitant use of fluticasone and CRIXIVAN® (indinavir sulfate) may increase plasma concentrations of fluticasone, particularly for long-term use. Use of fluticasone is not recommended in situations in which CRIXIVAN is coadministered with a potent CYP3A4 inhibitor such as ritonavir unless the potential benefit to the patient outweighs the risk of systemic corticosteroid adverse reactions.
HMG-CoA reductase inhibitor: atorvastatin	↑ atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors not primarily metabolized by CYP3A4, such as pravastatin, fluvastatin, or rosuvastatin, in combination with CRIXIVAN.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	Plasma concentrations may be increased by CRIXIVAN.
Itraconazole	↑ indinavir	Dose reduction of CRIXIVAN to 600 mg q8h is recommended.
Midazolam (parenteral administration)	↑ midazolam	Concomitant use of parenteral midazolam with CRIXIVAN may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with CRIXIVAN is CONTRAINDICATED.
Ketoconazole	↑ indinavir	Dose reduction of CRIXIVAN to 600 mg q8h should be considered.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and CRIXIVAN may increase plasma concentrations of trazodone. Nausea, dizziness, hypotension, and syncope have been observed after coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as CRIXIVAN, the combination should be used with caution, and a lower dose of trazodone should be considered.
Rifabutin	↓ indinavir, ↑ rifabutin	Dose reduction of rifabutin to half the standard dose and dose increase of CRIXIVAN to 1000 mg (three 333-mg capsules) q8h are recommended when rifabutin and CRIXIVAN are coadministered.

Erectile dysfunction agents: sildenafil, tadalafil, vardenafil	↑ erectile dysfunction agent	The dose of these agents should not exceed maximum dose according to the respective Prescribing Information when receiving concomitant indinavir therapy.
Venlafaxine	↓ indinavir	In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800-mg oral dose of indinavir and a 36% decrease in indinavir C _{max} . Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

Note: ↑ = increase; ↓ = decrease.

Selected Adverse Reactions

Selected adverse reactions of severe or life-threatening intensity and of unknown drug relationship reported by patients treated with CRIVAN® (indinavir sulfate)/AZT/3TC in ACTG 320 were fever (3.8%), nausea (2.8%), nephrolithiasis/uroolithiasis (2.6%), headache (2.4%), asthenia/fatigue (2.4%), anemia (2.4%), abdominal pain (1.9%), difficulty breathing/dyspnea/ shortness of breath (1.8%), cough (1.6%), vomiting (1.4%), rash (1.1%), back pain (0.9%), and diarrhea (0.9%).

Before prescribing ISENTRESS® (raltegravir) or CRIVAN, please read the accompanying Prescribing Information.

For additional copies of the Prescribing Information, call 1-800-672-6372, visit isentress.com, crxivan.com, or contact your Merck representative.

Sincerely,



Walter L. Straus, MD

Enclosures: Prescribing Information for ISENTRESS
Prescribing Information for CRIVAN