

Name of Medicine

CRIXIVAN[®]

indinavir sulfate

200 mg & 400 mg capsules

Presentation

CRIXIVAN 200 mg: A #1 white semi-translucent capsule with 'CRIXIVAN™ 200 mg' printed in blue ink. Each capsule contains 200 mg of indinavir (250 mg indinavir sulphate). Dimensions are approximately 19.4 mm in length and 6.91 mm in diameter.

CRIXIVAN 400 mg: A #00 white semi-translucent capsule with 'CRIXIVAN™ 400 mg' printed in green ink. Each capsule contains 400 mg of indinavir (500 mg indinavir sulfate). Dimensions are approximately 25.3 mm in length and 8.53 mm in diameter.

Therapeutic Class

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

Indications

CRIXIVAN is indicated for the treatment of adults with HIV-1 infection. Clinical studies demonstrated:

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

Dosage and Administration

The recommended dosage of CRIXIVAN is 800 mg (usually given as two 400 mg capsules) orally every 8 hours. Therapy with CRIXIVAN must be initiated at the recommended dose of 2.4 gm/day.

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

CRIXIVAN should be used:

- in combination with approved antiretroviral agents (e.g. nucleoside and non-nucleoside reverse transcriptase inhibitors), for the treatment of adult patients with HIV-1 infection.

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

To ensure adequate hydration, it is recommended that the patient drink at least 1.5 litres (approximately 48 ounces) of liquids during the course of 24 hours.

In addition to adequate hydration, medical management in patients with one or more episodes of nephrolithiasis may include temporary interruption of therapy (e.g., 1 to 3 days) during the acute episode of nephrolithiasis or discontinuation of therapy.

Concomitant Therapy

Rifabutin

Dose reduction of rifabutin to half the standard dose is recommended (consult the manufacturer's prescribing information for rifabutin) and a dose increase of CRIXIVAN to 1000 mg every 8 hours are recommended when rifabutin and CRIXIVAN are co-administered.

Ketoconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering ketoconazole concurrently.

Itraconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering itraconazole 200 mg twice daily concurrently.

Delavirdine

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day.

Patients with Coexisting Conditions

Hepatic Insufficiency Due to Cirrhosis

The dosage of CRIXIVAN should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

Contraindications

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

CRIXIVAN should not be administered concurrently with amiodarone, terfenadine, cisapride, astemizole, alprazolam, triazolam, midazolam administered orally (for parenterally administered midazolam, see Interactions), pimozide, ergot derivatives, lovastatin, or simvastatin. Inhibition of CYP3A4 by CRIXIVAN could result in elevated plasma concentration of these medicines, potentially causing serious or life-threatening reactions.

Warnings and Precautions

Nephrolithiasis

Nephrolithiasis has occurred with CRIXIVAN. 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 haematuria (including microscopic haematuria), 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 in all patients treated with CRIXIVAN. Consideration of dosage adjustment may be necessary. (See Adverse Effects, 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/higher power field). In patients with asymptomatic severe leukocyturia, further evaluation may be warranted.

Acute Haemolytic Anaemia

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

Hepatitis

Hepatitis including rare cases of hepatic failure have been reported in patients treated with CRIXIVAN. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapy(ies), a causal relationship between CRIXIVAN and these events has not been established.

Hyperglycaemia

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

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including CRIXIVAN. During the initial phase of treatment, a patient whose immune system responds to CART may mount an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

Medicine Interactions

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

Concomitant use of CRIXIVAN and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Co-administration of CRIXIVAN and St.

John's wort has been shown to substantially decrease indinavir concentrations and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

Both CRIXIVAN and atazanavir are associated with indirect (unconjugated) hyperbilirubinaemia. Combinations of these medicines have not been studied and co-administration of CRIXIVAN and atazanavir is not recommended.

Patients with Coexisting Conditions

There have been reports of spontaneous bleeding in patients with haemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (See Adverse Effects, Post-Marketing Experience.)

Patients with hepatic insufficiency due to cirrhosis

In these patients, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN.

Pregnancy

There are no adequate and well controlled studies in pregnant patients. CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Given substantially lower antepartum exposures 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.

Distribution of indinavir across the placental barrier was significant in rats and dogs but limited in rabbits.

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

Hyperbilirubinaemia has occurred in both healthy subjects and HIV-1 infected patients treated with various dosage levels of CRIXIVAN and has rarely been associated with increases in serum transaminases. However, because of the theoretical potential for the compound to exacerbate the physiologic hyperbilirubinaemia seen in human neonates, careful consideration must be given to the use of CRIXIVAN in pregnant women at the time of delivery.

Nursing Mothers

It is not known whether CRIXIVAN is excreted in human milk. Because many medicines are excreted in human milk, and because of the potential for adverse reactions from CRIXIVAN in nursing infants, mothers should be instructed to discontinue nursing if they are receiving CRIXIVAN.

Excretion of indinavir into the milk of lactating rats was extensive with the ratio of indinavir in milk to that in plasma averaging 1.26 to 1.45.

Paediatric Use

Safety and effectiveness in children have not been established.

Effects on Ability to Use and Drive Machines

There are no data to suggest that CRIXIVAN affects the ability to drive and use machines.

Animal Toxicology

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 vitro* mammalian cell mutagenesis assays.

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumour 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.

Development

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 ≥ 160 mg/kg/day (at or below human exposure) and of cervical ribs at 640 mg/kg/day (comparable to or slightly greater than human exposure) 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/foetal survival or foetal weights were observed. *In utero* exposure to indinavir was significant in rats and dogs, but low in rabbits.

Studies in which rats were administered 40 or 640 mg/kg/day demonstrated that indinavir is excreted in milk of lactating rats.

Adverse Effects

Clinical trials

In controlled clinical trials conducted worldwide, CRIXIVAN was administered alone or in combination with other antiretroviral agents (zidovudine, didanosine, and/or lamivudine) and was found to be generally well tolerated.

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

The majority of these adverse experiences with CRIXIVAN were of mild intensity and did not result in discontinuation of treatment. Discontinuation of therapy due to any clinical adverse experience occurred in 5.1% of 196 patients treated with CRIXIVAN alone, 5.7% of 53 patients treated with CRIXIVAN in combination with other antiretroviral agents, and in 6.8% of 74 patients treated with other antiretroviral agents alone.

Clinical adverse experiences reported by the investigators as possibly, probably, or definitely medicine related in $\geq 5\%$ of patients, without regard to severity, treated with

CRIXIVAN alone (n=196), were: asthenia/fatigue, abdominal pain, acid regurgitation, diarrhoea, dry mouth, dyspepsia, flatulence, nausea, vomiting, lymphadenopathy, dizziness, headache, hypesthesia, insomnia, dry skin, pruritus, rash, taste perversion. Many of the most common adverse experiences were also identified as a common pre-existing or frequently occurring medical conditions in this population.

In clinical trials with CRIXIVAN, nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), 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, *Nephrolithiasis*, and Dosage and Administration.)

Post-Marketing Experience

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

Body As A Whole/Site Unspecified: Abdominal distention, redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen, and retroperitoneum.

Cardiovascular System: Cardiovascular disorders including myocardial infarction and angina pectoris; cerebrovascular disorder.

Digestive System: Liver function abnormalities; hepatitis including rare reports of hepatic failure (see Warnings and Precautions); pancreatitis.

Haematologic: Increased spontaneous bleeding in patients with haemophilia; thrombocytopenia; anaemia including acute haemolytic anaemia (see Warnings and Precautions).

Endocrine/Metabolic: New onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus (see Warnings and Precautions).

Hypersensitivity: Anaphylactoid reactions; vasculitis.

Nervous Systems/Psychiatric: Oral paresthesia.

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

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

Laboratory Test Findings

The most frequently occurring laboratory adverse experiences (Incidence $\geq 5\%$) considered by the investigator to be possibly, probably, or definitely medicine related in the group treated with CRIXIVAN 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 CRIXIVAN alone or in combination with other antiretroviral agents.

Isolated asymptomatic hyperbilirubinaemia (total bilirubin ≥ 2.5 mg/dl), reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has occurred in patients treated with CRIXIVAN alone or in combination with other antiretroviral agents. Most patients continued treatment with CRIXIVAN without dosage reduction and bilirubin values gradually declined toward baseline.

Post Marketing Experience

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

Interactions

Specific medicine interaction studies were performed with indinavir and the following medicines including: zidovudine/lamivudine, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, clarithromycin, methadone or an oral contraceptive (norethindrone/ethinyl estradiol 1/35). No clinically significant interactions were observed with these medicines. However, clinically significant interactions with other medicines are described below.

Pimozide

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

Rifampin

Rifampin is a potent inducer of P450 3A4 which markedly diminishes plasma concentrations of indinavir. Therefore, CRIXIVAN and rifampin should not be co-administered.

Rifabutin

Due to an increase in the plasma concentrations of rifabutin and a decrease in the plasma concentrations of indinavir, a dosage reduction of rifabutin and a dosage increase of CRIXIVAN are necessary when rifabutin is co-administered with CRIXIVAN (see Dosage and Administration).

Ketoconazole

Due to an increase in the plasma concentrations of indinavir, a dosage reduction of indinavir should be considered when indinavir and ketoconazole are co-administered.

Itraconazole

Itraconazole is an inhibitor of P-450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN and itraconazole are co-administered. (See Dosage and Administration.)

Delavirdine

Due to an increase in indinavir plasma concentration, a dosage reduction of indinavir should be considered when CRIXIVAN and delavirdine are co-administered. (See Dosage and Administration.)

Efavirenz

When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily) in uninfected volunteers, the indinavir AUC, C_{max} , and C_{min} were decreased by approximately 33-46%, 5-29%, and 39-57% respectively, compared to when indinavir was given alone at the standard dose (800 mg every 8 hours). Similar

differences in indinavir AUC, C_{max} , and C_{min} were also observed in HIV-infected subjects who received indinavir (1000 mg every 8 hours) with efavirenz (600 mg once daily) compared to indinavir given alone (800 mg every 8 hours). The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.

Ritonavir

Twice daily co-administration to volunteers of indinavir (800 mg) and ritonavir (100, 200, or 400 mg) with food for two weeks resulted in indinavir AUC_{24h} increases of 178%, 266%, and 220%, respectively, compared to historical indinavir AUC_{24h} values in patients who received CRIXIVAN 800 mg every 8 hours alone. In addition, twice daily co-administration of indinavir (400 mg) and ritonavir (400 mg) resulted in indinavir AUC_{24h} increases of 68%. In the same study, twice daily co-administration of indinavir (800 mg) and ritonavir (100 or 200 mg) resulted in ritonavir AUC_{24h} increases of 72% and 96%, respectively, versus the same doses of ritonavir alone. By contrast, twice daily co-administration of indinavir (800 or 400 mg) and ritonavir (400 mg) had a negligible effect (7% and 7% decreases, respectively) on ritonavir AUC_{24h} . In cases of co-administration of ritonavir and indinavir (dosed at 800 mg twice daily), caution is warranted as the risk of nephrolithiasis can be increased. Appropriate hydration is recommended.

Atazanavir

Both CRIXIVAN and atazanavir are associated with indirect (unconjugated) hyperbilirubinaemia. Combinations of these medicines have not been studied and coadministration of CRIXIVAN and atazanavir is not recommended.

HMG-CoA Reductase Inhibitors

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

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

Concomitant use of CRIXIVAN and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Co-administration of CRIXIVAN and St. John's wort has been shown to substantially decrease indinavir concentrations and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

Venlafaxine

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

Other

Medicines Metabolised by CYP3A4

Co-administration of CRIXIVAN, a CYP3A4 inhibitor, with calcium channel blockers, trazodone and other medicines metabolised by CYP3A4, may result in increased plasma concentrations of these medicines which could increase or prolong their therapeutic and adverse effects.

Midazolam

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

If indinavir and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach.

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

PDE5 Inhibitors

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

Overdosage

There have been more than 60 reports of acute or chronic human overdosage (up to 23 times the recommended total daily dose of 2400 mg) with CRIXIVAN. The most commonly reported symptoms were renal (e.g., nephrolithiasis, flank pain, haematuria) and gastrointestinal (e.g., nausea, vomiting, diarrhoea).

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.

Actions

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

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

Microbiology

Indinavir at concentrations of 50 to 100 nM mediated 95% inhibition (IC_{95}) of viral spread (relative to an untreated virus-infected control) in human T-lymphoid cell cultures infected with several cell-line adapted variants of HIV-1 (LAI, MN, and RF). Similar inhibition of HIV-1 infection was seen in primary human monocytes/macrophages using a macrophage-tropic viral variant (SF 162). In addition, indinavir at concentrations of 25 to 100 nM resulted in 95% inhibition 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.

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.

Cross Resistance

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

Pharmacokinetics

Absorption

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

continuous dosing at 600 mg every 6 hours. The bioavailability of a single 800 mg dose of indinavir was approximately 65%.

Effect of Food on Oral Absorption

Administration of indinavir with a meal high in calories, fat, and protein resulted in a blunted and reduced absorption, with an approximate 80% reduction in AUC and an 85% reduction in C_{max} . Administration with light meals (e.g., dry toast with jam, apple juice, and coffee with skim milk and sugar) resulted in a 2-8% reduction in AUC and C_{max} . The plasma concentrations six and eight hours after administration of indinavir with light meals were comparable to the corresponding fasted values.

Distribution

Indinavir was not highly bound to human plasma proteins (39% unbound). Uptake into rat brain tissue was shown to be limited and the ratio of medicine concentration in the brain to that in plasma averaged 0.18. Distribution into and out of the rat lymphatic system was shown to be rapid.

Metabolism

Indinavir metabolism was evaluated in healthy subjects who received 400 mg and 1000 mg oral doses. Approximately 83% and 19% of the total radioactivity was recovered in the faeces and urine, respectively, following a 400 mg ^{14}C -radiolabelled dose. *In vitro* studies with human liver microsomes indicated that cytochrome CYP3A4 is the only P450 isozyme that plays a major role in the oxidative metabolism of indinavir. Analysis of plasma and urine samples from subjects who received indinavir indicated that indinavir metabolites contribute little to the overall *in vivo* protease inhibitory activity.

Elimination

Less than 20% of indinavir is excreted unchanged renally. Mean urinary excretion of unchanged medicine following single dose administration in the fasted state was 10.4% following a 700 mg dose, and 12.0% following a 1000 mg dose. Indinavir was rapidly eliminated with a half-life of 1.8 hours.

Characteristics in Patients

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. The mean half-life of indinavir increased to approximately 2.8 hours. Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

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

Gender

Pharmacokinetics of indinavir appear to be comparable in men and women. These findings are based on a pharmacokinetic study in 10 HIV seropositive women who received CRIVAN 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for one week. There were no clinically significant differences in the indinavir pharmacokinetic parameters in these women compared to HIV seropositive men (pooled historical control data).

Race

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

Elderly Patients

Safety and effectiveness in elderly patients has not been established.

Pharmaceutical Precautions

Store in a tightly-closed container at room temperature, below 30°C (86°F). 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.

Medicine Classification

Prescription Medicine

Package Quantities

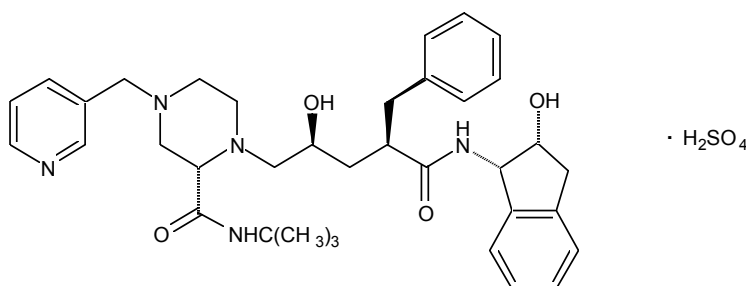
200 mg capsules are available in bottles of 360 capsules.

400 mg capsules are available in bottles of 180 capsules.

Further Information

Chemistry

The chemical name for indinavir is [1(1*S*,2*R*),5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-*D*-*erythro*-pentonamide sulfate (1:1) salt. Indinavir sulfate has the following structural formula:



Indinavir sulfate is a white to off-white, free-flowing crystalline powder with the molecular formula C₃₆H₄₇N₅O₄·H₂SO₄ and a molecular weight of 711.88.

Composition

Active Ingredients

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

Inactive Ingredients

Each capsule also contains the inactive ingredients anhydrous lactose (acting as a diluent) and magnesium stearate (as a lubricant). The capsule excipients are gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.

Name and Address

Merck Sharp & Dohme (New Zealand) Limited
P O Box 99 851
Newmarket
Auckland
NEW ZEALAND
Tel: 0800 500 673

Date of Preparation

16 December 2011

DP-CRX- 112011(161211)

®Registered Trademark of Merck & Co Inc., Whitehouse Station, NJ, USA
Copyright© 2009 Merck & Co., Inc. All rights reserved