ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
CRIXIVAN 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
CRIXIVAN 200 mg capsules contain 250 mg of indinavir sulphate corresponding to 200 mg of indinavir.

3. PHARMACEUTICAL FORM
Capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
CRIXIVAN is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected adult patients with advanced or progressive immunodeficiency.

The combinations with zidovudine, zidovudine/didanosine and zidovudine/lamivudine reduce viral load in serum and increase CD4 cell counts. A preliminary analysis from early and ongoing studies indicates that indinavir slows progression of disease. Clinical studies are underway to confirm the clinical benefits of indinavir.

See section 5.1 for pharmacodynamic results.

4.2 Posology and method of administration
The recommended dosage of CRIXIVAN is 800 mg orally every 8 hours.

CRIXIVAN should be used in combination with other antiretroviral agents (i.e. nucleoside analogues).

The capsules should be swallowed whole.

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 a low-fat, light meal.

To ensure adequate hydration, it is recommended that the patient drinks at least 1.5 liters of liquids during the course of 24 hours.

Due to an increase in the plasma concentrations of indinavir, a dosage reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering ketoconazole concurrently.

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

Medical management in patients with one or more episodes of nephrolithiasis must include adequate hydration and may include consideration of dosage reduction to 600 mg every 8 hours. Although this dosage may be associated with a decreased risk of nephrolithiasis, it may also be associated with a decrease in the antiretroviral activity of indinavir. Therefore, the potential risks and benefits of dosage reduction should be carefully considered. See also section 5.1.

4.3 Contra-indications
Clinically significant hypersensitivity to any component of this product.
Indinavir should not be administered concurrently with drugs with narrow therapeutic windows and which are substrates of CYP3A4. Co-administration may result in competitive inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmias (e.g., terfenadine, astemizole, cisapride) prolonged sedation or respiratory depression (e.g., alprazolam, triazolam, midazolam).

4.4 Special warnings and special precautions for use

Manifestations of nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), have been reported in 2.6% of patients (55/2077) receiving the recommended dose of CRIXIVAN (2.4 g daily) and 7% of patients (7/100) receiving CRIXIVAN in doses above 2.4 g daily. Adequate hydration is recommended in all patients on CRIXIVAN (see Posology and method of administration).

Patients with mild to moderate hepatic insufficiency due to cirrhosis will require a dosage reduction of CRIXIVAN due to decreased metabolism of indinavir (see Posology and method of administration). Patients with severe hepatic impairment have not been studied. In the absence of such studies, caution should be exercised as increased levels of indinavir may occur.

Safety in patients with impaired renal function has not been studied; however, less than 20% of indinavir is excreted in the urine as unchanged drug or metabolites.

In clinical trials, the majority of investigated patients were Caucasian males.

Safety and effectiveness in children have not been established.

In clinical trials, patients treated with rifampicin, rifabutin, or chronically with acyclovir were excluded. However, patients treated intermittently with acyclovir were not excluded from the clinical trials.

Each capsule contains 74 mg lactose (anhydrous). This quantity is probably not sufficient to induce specific symptoms of intolerance.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies were performed with indinavir and the following drugs: zidovudine, zidovudine/lamivudine, stavudine, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, clarithromycin, quinidine, cimetidine, and an oral contraceptive (norethindrone/ethinyl estradiol 1/35). No clinically significant interactions were observed with these drugs. Clinically significant interactions with other drugs are described below.
Rifabutin
A clinically significant drug interaction was observed with rifabutin. Administration of indinavir at a dose of 800 mg every 8 hours with rifabutin at a dose of 300 mg once daily for 10 days resulted in a 34% decrease in AUC and a 25% decrease in Cmax of indinavir. In contrast, the AUC of rifabutin increased about 173% and the Cmax of rifabutin increased about 134%, a clinically significant interaction. This increase in rifabutin plasma concentrations is likely related to inhibition of CYP3A4-mediated metabolism of rifabutin by indinavir. A dosage reduction of rifabutin to half the standard dose is necessary when indinavir and rifabutin are coadministered.

Ketoconazole
Administration of a 400 mg dose of ketoconazole, a potent inhibitor of CYP3A4, with a 400 mg dose of indinavir resulted in a 62% increase in the AUC of indinavir, which is clinically significant, and a 14% increase in the Cmax of indinavir. A dosage reduction of Indinavir to 600 mg every 8 hours should be considered when indinavir and ketoconazole are coadministered.

Rifampicin
Pharmacokinetic data from an interaction study with rifampicin is not yet available. Because rifampicin is a potent inducer of CYP3A4 which could markedly diminish plasma concentrations of indinavir, coadministration of indinavir and rifampicin is not recommended.

Other
A formal drug interaction study between indinavir and methadone has not been performed. Concomitant use may result in increased plasma concentrations of methadone. The clinical relevance of this is unknown.

A formal drug interaction study between indinavir and itraconazole has not been performed. Because itraconazole is a potent inhibitor of CYP3A4, concomitant use could result in clinically significant increases in plasma concentrations of indinavir.

Concomitant use of other drugs that are inducers of CYP3A4, such as phenobarbital, phenytoin, dexamethasone and carbamazapine, may reduce indinavir plasma concentrations.

The efficacy and safety of indinavir in combination with other protease inhibitors have not been established. Coadministration with ritonavir is likely to result in significant increases in plasma concentrations of indinavir.

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

For optimal absorption, indinavir should be administered with water 1 hour before or 2 hours after a meal. Alternatively, indinavir may be taken with a low-fat light meal. Ingestion of indinavir with a meal high in calories, fat and protein reduces the absorption of indinavir.
4.6 Use during pregnancy and lactation

Use during pregnancy
CRIXIVAN has not been studied in pregnant women. Until additional data become available, CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hyperbilirubinaemia, reported predominantly as elevated indirect bilirubin, has occurred in 10% of patients during treatment with CRIXIVAN. Because it is unknown whether indinavir will exacerbate physiologic hyperbilirubinaemia in neonates, careful consideration must be given to the use of CRIXIVAN in pregnant women at the time of delivery (see Undesirable effects).

Developmental toxicity studies performed in rats and rabbits at doses 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 in the incidence of supernumerary ribs (at or below human exposure) and of cervical ribs (doses comparable to or slightly greater than human exposure) were seen in rats. No treatment-related external, visceral, or skeletal changes were observed in rabbits. In both species, no treatment-related abortions or effects on embryonic/fetal survival or fetal weights were observed.

Use during lactation
Health experts recommend that HIV-infected women should not breast feed their infants under any circumstances in order to avoid transmission of HIV. It is not known whether indinavir is excreted in human milk. However, indinavir was shown to be present in rat milk and excretion in rat milk was also manifested as decreased pup weight gain during lactation. Until more data become available, mothers should be instructed to discontinue breast feeding during treatment.

4.7 Effects on ability to drive and use machines

There are no data to suggest that indinavir affects the ability to drive and use machines. However, patients should be informed that dizziness and blurred vision have been reported during treatment with indinavir.

4.8 Undesirable effects

In controlled clinical trials conducted worldwide, indinavir was administered alone or in combination with other antiretroviral agents (zidovudine, didanosine, stavudine, and/or lamivudine) to approximately 2,000 patients, the majority of whom were Caucasian males (15% females).

Indinavir did not alter the type, frequency, or severity of known major adverse effects associated with the use of zidovudine, didanosine, or lamivudine.

Clinical adverse experiences reported by the investigators as possibly, probably, or definitely drug related in ≥5% of patients treated with CRIXIVAN alone or in combination (n= 309) for 24 weeks are listed below. Many of these adverse experiences were also identified as common pre-existing or frequently occurring medical conditions in this population. These adverse experiences were: nausea (35.3%), headache (25.2%), diarrhea (24.6%), asthenia/fatigue (24.3%), rash (19.1%), taste perversion (19.1%), dry skin (16.2%), abdominal pain (14.6%), vomiting (11.0%), dizziness (10.7%), dyspepsia (10.7%), flatulence (7.8%), insomnia (7.4%), pruritus (7.4%), hypesthesia (7.1%), dry mouth (6.8%), dysuria (6.5%), acid regurgitation (6.5%), paresthesia (5.2%), and myalgia (5.2%). With the exception of dry skin, rash, and taste perversion, the incidence of clinical adverse experiences was similar or higher among patients treated with antiretroviral nucleoside analogue controls than among patients treated with CRIXIVAN alone or in combination. This overall safety profile remained similar for 107 patients treated with CRIXIVAN alone or in combination for up to 48 weeks.

Nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), has been reported in 2.6% (55/2077) of patients receiving CRIXIVAN alone or in combination with other antiretroviral agents. These episodes were assumed to be drug related and were not associated with renal
dysfunction. Nephrolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

Laboratory Test Findings
The laboratory abnormalities reported by the investigators as possibly, probably, or definitely drug related in ≥10% of patients treated with CRIXIVAN alone or in combination were: increases in MCV, ALT, AST, indirect bilirubin, total serum bilirubin; a decrease in neutrophils; haematuria, proteinuria, crystalluria.

Isolated asymptomatic hyperbilirubinaemia (total bilirubin ≥2.5 mg/dl, 43 mcmol/l), reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has occurred in approximately 10% of patients treated with 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. Hyperbilirubinemia occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

4.9 Overdose
No reports are available with regard to overdosage in humans. It is not known whether indinavir is dialyzable by peritoneal or hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiviral agent, ATC code J05AX07

Mechanism of Action
Indinavir inhibits recombinant HIV-1 and HIV-2 protease with an approximate tenfold selectivity for HIV-1 over HIV-2 proteinase. Indinavir binds reversibly to the protease active site and inhibits competitively the enzyme, thereby preventing cleavage of the viral precursor polyproteins 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 the eukaryotic proteases human renin, human cathepsin D, human elastase, and human factor Xa.

Microbiology
Indinavir at concentrations of 50 to 100 nM mediated 95% inhibition (IC50) of viral spread (relative to an untreated virus-infected control) in human T-lymphoid cell cultures and primary human monocytes/macrophages infected with HIV-1 variants LAI, MN, RF, and a macrophage-tropic variant SF-162, respectively. Indinavir at concentrations of 25 to 100 nM mediated 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 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.

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. 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 CRIXIVAN was initiated at doses lower than the recommended oral dose of 2.4 g/day. Therefore, therapy with CRIXIVAN should be initiated at the recommended dose to increase suppression of viral replication and therefore inhibit the emergence of resistant virus.

The concomitant use of indinavir with nucleoside analogues (to which the patient is naive) may lessen the risk of the development of resistance to both indinavir and the nucleoside analogues. In one comparative trial, combination therapy with nucleoside analogues (triple therapy with zidovudine plus didanosine) conferred protection against the selection of virus expressing at least one resistance-associated amino acid substitution to both indinavir (from 13/24 to 2/20 at therapy week 24) and to the nucleoside analogues (from 10/16 to 0/20 at therapy week 24).

Combination treatment with CRIXIVAN is preferred because of the concern about the emergence of resistance.

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.

Pharmacodynamic Effects
Treatment with indinavir alone or in combination with other antiretroviral agents (i.e., nucleoside analogues) has so far been documented to reduce viral load and increase CD4 lymphocytes in patients with CD4 cell counts below 500 cells/mm³.

The effects of indinavir (alone or combined with other antiretroviral agents) on the biological markers of disease activity, CD4 cell counts and serum viral RNA, were evaluated in several studies involving HIV-1 seropositive patients with CD4 cell counts <500 cells/mm³. These studies have documented that indinavir, 2.4 g/day was consistently associated with increases in median CD4 cell counts of 90-100 cells/mm³ and median declines in serum viral RNA in excess of 1 log₁₀ copies/ml which were sustained to at least 24 weeks. Approximately 40% of these patients had serum viral RNA levels decrease to below 500 copies/ml, the limit of detection of the assay.

In one study at 24 weeks, the median declines in serum viral RNA for the group treated with indinavir alone, the group treated with indinavir in combination with zidovudine and lamivudine, and the group treated with zidovudine plus lamivudine were 0.67 log₁₀ (89%), 1.88 log₁₀ (98%), and 0.66 log₁₀ (78%), respectively. At 24 weeks, the percentage of patients whose serum viral RNA levels had decreased to below the limit of detection of the assay (<500 copies/ml) were 35% and 91%, for the groups treated with indinavir alone or in combination, respectively. A total of 0% of the patients in the zidovudine plus lamivudine group experienced this level of serum viral RNA decline at the 24 week time point. Median CD4 cell counts at 24 weeks were increased for all treatment groups.
5.2 Pharmacokinetic properties

Absorption
Indinavir is rapidly absorbed in the fasted state with a time to peak plasma concentration of 0.8 hours ± 0.3 hours (mean ± S.D.). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-800 mg dose range. Between 800-mg and 1000-mg dose levels, the deviation from dose-proportionality is less pronounced. As a result of the short half-life, 1.8 ± 0.4 hours, only a minimal increase in plasma concentrations occurred after multiple dosing.

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 86% reduction in $C_{\text{max}}$. Administration with light meals (e.g., dry toast with jam or fruit conserve, apple juice, and coffee with skimmed or fat-free milk and sugar or corn flakes, skimmed or fat-free milk and sugar) resulted in plasma concentrations comparable to the corresponding fasted values.

Distribution
Indinavir was not highly bound to human plasma proteins (39% unbound).

There are no data concerning the penetration of indinavir into the central nervous system in humans.

Biotransformation
Seven major metabolites were identified and the metabolic pathways were identified as glucuronidation at the pyridine nitrogen, pyridine-N-oxidation with and without 3’-hydroxylation on the indane ring, 3’-hydroxylation of indane, p-hydroxylation of phenylmethyl moiety, and N-depyridomethylation with and without the 3’-hydroxylation. *In vitro* studies with human liver microsomes indicated that 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 had little protease inhibitory activity.

Elimination
Over the 200-1000 mg dose range administered in both volunteers and HIV infected patients, there was a slightly greater than dose-proportional increase in urinary recovery of indinavir. Renal clearance (116 ml/min) of indinavir is concentration-independent over the clinical dose range. Less than 20% of indinavir is excreted renally. Mean urinary excretion of unchanged drug 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
Pharmacokinetics of indinavir do not appear to be affected by gender or by race.

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 400-mg dose. The mean half-life of indinavir increased to approximately 2.8 hours.

At steady state following a dosage regimen of 800 mg every 8 hours, HIV-seropositive patients in one study achieved AUC values of 28,713 nMh, peak plasma concentrations of 11,144 nM and plasma concentrations at 8 hours post dose of 211 nM.
5.3 Preclinical Safety Data

Crystals have been seen in the urine of rats, one monkey, and one dog. The crystals have not been associated with drug-induced renal injury. 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.

The maximum non-lethal oral dose of indinavir was at least 5000 mg/kg in rats and mice, the highest dose tested in acute toxicity studies.

Studies in rats indicated that uptake into brain tissue was limited, distribution into and out of the lymphatic system was rapid, and excretion into the milk of lactating rats was extensive. Distribution of indinavir across the placental barrier was significant in rats, but limited in rabbits.

Mutagenicity: Indinavir did not have any mutagenic or genotoxic activity in studies with or without metabolic activation.

Carcinogenicity: Carcinogenicity studies of indinavir are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains the excipients anhydrous lactose and magnesium stearate. The capsule shell contains the excipients gelatine, titanium dioxide, silicon dioxide, and sodium lauryl sulphate. The 200-mg capsules are printed with printing ink containing titanium dioxide (E 171) and indigo carmine (E 132).

The capsules are white opaque and coded CRIXIVAN™ 200 mg in blue.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The shelf-life is 12 months.

6.4 Special precautions for storage

Sensitive to moisture. Store in a well-closed container.

6.5 Nature and contents of container

CRIXIVAN 200 mg is supplied in HDPE bottles with a polypropylene cap and a foil induction cap containing 180, 270 or 360 capsules.

The containers contain desiccant canisters that should remain in the bottle. Patients should be advised not to swallow desiccant.
7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

CRIXIVAN 400 mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

CRIXIVAN 400 mg capsules contain 500 mg of indinavir sulphate corresponding to 400 mg of indinavir.

3. **PHARMACEUTICAL FORM**

Capsules.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

CRIXIVAN is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected adult patients with advanced or progressive immunodeficiency.

The combinations with zidovudine, zidovudine/didanosine and zidovudine/lamivudine reduce viral load in serum and increase CD4 cell counts. A preliminary analysis from early and ongoing studies indicates that indinavir slows progression of disease. Clinical studies are underway to confirm the clinical benefits of indinavir.

See section 5.1 for pharmacodynamic results.

4.2 **Posology and method of administration**

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CRIXIVAN should be used in combination with other antiretroviral agents (i.e. nucleoside analogues).

The capsules should be swallowed whole.

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 a low-fat, light meal.

To ensure adequate hydration, it is recommended that the patient drinks at least 1.5 liters of liquids during the course of 24 hours.

Due to an increase in the plasma concentrations of indinavir, a dosage reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering ketoconazole concurrently.

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

Medical management in patients with one or more episodes of nephrolithiasis must include adequate hydration and may include consideration of dosage reduction to 600 mg every 8 hours. Although this dosage may be associated with a decreased risk of nephrolithiasis, it may also be associated with a decrease in the antiretrovirial activity of indinavir. Therefore, the potential risks and benefits of dosage reduction should be carefully considered. See also section 5.1.
4.3 Contra-indications

Clinically significant hypersensitivity to any component of this product.

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

4.4 Special warnings and special precautions for use

Manifestations of nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), have been reported in 2.6% of patients (55/2077) receiving the recommended dose of CRIXIVAN (2.4 g daily) and 7% of patients (7/100) receiving CRIXIVAN in doses above 2.4 g daily. Adequate hydration is recommended in all patients on CRIXIVAN (see Posology and method of administration).

Patients with mild to moderate hepatic insufficiency due to cirrhosis will require a dosage reduction of CRIXIVAN due to decreased metabolism of indinavir (see Posology and method of administration). Patients with severe hepatic impairment have not been studied. In the absence of such studies, caution should be exercised as increased levels of indinavir may occur.

Safety in patients with impaired renal function has not been studied; however, less than 20% of indinavir is excreted in the urine as unchanged drug or metabolites.

In clinical trials, the majority of investigated patients were Caucasian males.

Safety and effectiveness in children have not been established.

In clinical trials, patients treated with rifampicin, rifabutin, or chronically with acyclovir were excluded. However, patients treated intermittently with acyclovir were not excluded from the clinical trials.

Each capsule contains 149 mg lactose (anhydrous). This quantity is probably not sufficient to induce specific symptoms of intolerance.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies were performed with indinavir and the following drugs: zidovudine, zidovudine/lamivudine, stavudine, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, clarithromycin, quinidine, cimetidine, and an oral contraceptive (norethindrone/ethinyl estradiol 1/35). No clinically significant interactions were observed with these drugs. Clinically significant interactions with other drugs are described below.
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Ketoconazole
Administration of a 400 mg dose of ketoconazole, a potent inhibitor of CYP3A4, with a 400 mg dose of Indinavir resulted in a 62% increase in the AUC of indinavir, which is clinically significant, and a 14% increase in the Cmax of indinavir. A dosage reduction of Indinavir to 600 mg every 8 hours should be considered when indinavir and ketoconazole are coadministered.

Rifampicin
Pharmacokinetic data from an interaction study with rifampicin is not yet available. Because rifampicin is a potent inducer of CYP3A4 which could markedly diminish plasma concentrations of indinavir, coadministration of indinavir and rifampicin is not recommended.

Other
A formal drug interaction study between indinavir and methadone has not been performed. Concomitant use may result in increased plasma concentrations of methadone. The clinical relevance of this is unknown.

A formal drug interaction study between indinavir and itraconazole has not been performed. Because itraconazole is a potent inhibitor of CYP3A4, concomitant use could result in clinically significant increases in plasma concentrations of indinavir.

Concomitant use of other drugs that are inducers of CYP3A4, such as phenobarbital, phenytoin, dexamethasone and carbamazepine, may reduce indinavir plasma concentrations.

The efficacy and safety of indinavir in combination with other protease inhibitors have not been established. Coadministration with ritonavir is likely to result in significant increases in plasma concentrations of indinavir.

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

For optimal absorption, indinavir should be administered with water 1 hour before or 2 hours after a meal. Alternatively, indinavir may be taken with a low-fat light meal. Ingestion of indinavir with a meal high in calories, fat and protein reduces the absorption of indinavir.
4.6 Use during pregnancy and lactation

Use during pregnancy
CRIXIVAN has not been studied in pregnant women. Until additional data become available, CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hyperbilirubinaemia, reported predominantly as elevated indirect bilirubin, has occurred in 10% of patients during treatment with CRIXIVAN. Because it is unknown whether indinavir will exacerbate physiologic hyperbilirubinaemia in neonates, careful consideration must be given to the use of CRIXIVAN in pregnant women at the time of delivery (see Undesirable effects).

Developmental toxicity studies performed in rats and rabbits at doses 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 in the incidence of supernumerary ribs (at or below human exposure) and of cervical ribs (doses comparable to or slightly greater than human exposure) were seen in rats. No treatment-related external, visceral, or skeletal changes were observed in rabbits. In both species, no treatment-related abortions or effects on embryonic/fetal survival or fetal weights were observed.

Use during lactation
Health experts recommend that HIV-infected women should not breast feed their infants under any circumstances in order to avoid transmission of HIV. It is not known whether indinavir is excreted in human milk. However, indinavir was shown to be present in rat milk and excretion in rat milk was also manifested as decreased pup weight gain during lactation. Until more data become available, mothers should be instructed to discontinue breast feeding during treatment.

4.7 Effects on ability to drive and use machines

There are no data to suggest that indinavir affects the ability to drive and use machines. However, patients should be informed that dizziness and blurred vision have been reported during treatment with indinavir.

4.8 Undesirable effects

In controlled clinical trials conducted worldwide, indinavir was administered alone or in combination with other antiretroviral agents (zidovudine, didanosine, stavudine, and/or lamivudine) to approximately 2,000 patients, the majority of whom were Caucasian males (15% females).

Indinavir did not alter the type, frequency, or severity of known major adverse effects associated with the use of zidovudine, didanosine, or lamivudine.

Clinical adverse experiences reported by the investigators as possibly, probably, or definitely drug related in ≥5% of patients treated with CRIXIVAN alone or in combination (n=309) for 24 weeks are listed below. Many of these adverse experiences were also identified as common pre-existing or frequently occurring medical conditions in this population. These adverse experiences were: nausea (35.3%), headache (25.2%), diarrhea (24.6%), asthenia/fatigue (24.3%), rash (19.1%), taste perversion (19.1%), dry skin (16.2%), abdominal pain (14.6%), vomiting (11.0%), dizziness (10.7%), dyspepsia (10.7%), flatulence (7.8%), insomnia (7.4%), pruritus (7.4%), hypesthesia (7.1%), dry mouth (6.8%), dysuria (6.5%), acid regurgitation (6.5%), paresthesia (5.2%), and myalgia (5.2%). With the exception of dry skin, rash, and taste perversion, the incidence of clinical adverse experiences was similar or higher among patients treated with antiretroviral nucleoside analogue controls than among patients treated with CRIXIVAN alone or in combination. This overall safety profile remained similar for 107 patients treated with CRIXIVAN alone or in combination for up to 48 weeks.

Nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), has been reported in 2.6% (55/2077) of patients receiving CRIXIVAN alone or in combination with other antiretroviral agents. These episodes were assumed to be drug related and were not associated with renal
dysfunction. Nephrolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

Laboratory Test Findings

The laboratory abnormalities reported by the investigators as possibly, probably, or definitely drug related in ≥10% of patients treated with CRIXIVAN alone or in combination were: increases in MCV, ALT, AST, indirect bilirubin, total serum bilirubin; a decrease in neutrophils; haematuria, proteinuria, crystalluria.

Isolated asymptomatic hyperbilirubinaemia (total bilirubin ≥2.5 mg/dl, 43 mcmol/l), reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has occurred in approximately 10% of patients treated with 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. Hyperbilirubinemia occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

4.9 Overdose

No reports are available with regard to overdosage in humans. It is not known whether indinavir is dialyzable by peritoneal or hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code JO5AX07

Mechanism of Action

Indinavir inhibits recombinant HIV-1 and HIV-2 protease with an approximate tenfold selectivity for HIV-1 over HIV-2 proteinase. Indinavir binds reversibly to the protease active site and inhibits competitively the enzyme, thereby preventing cleavage of the viral precursor polyproteins 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 the eukaryotic proteases human renin, human cathepsin D, human elastase, and human factor Xa.

Microbiology

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 and primary human monocytes/macrophages infected with HIV-1 variants LAI, MN, RF, and a macrophage-tropic variant SF-162, respectively. Indinavir at concentrations of 25 to 100 nM mediated 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 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.

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. 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 CRIXIVAN was initiated at doses lower than the recommended oral dose of 2.4 g/day. Therefore, therapy with CRIXIVAN should be initiated at the recommended dose to increase suppression of viral replication and therefore inhibit the emergence of resistant virus.

The concomitant use of indinavir with nucleoside analogues (to which the patient is naive) may lessen the risk of the development of resistance to both indinavir and the nucleoside analogues. In one comparative trial, combination therapy with nucleoside analogues (triple therapy with zidovudine plus didanosine) conferred protection against the selection of virus expressing at least one resistance-associated amino acid substitution to both indinavir (from 13/24 to 2/20 at therapy week 24) and to the nucleoside analogues (from 10/16 to 0/20 at therapy week 24).

Combination treatment with CRIXIVAN is preferred because of the concern about the emergence of resistance.

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.

Pharmacodynamic Effects
Treatment with indinavir alone or in combination with other antiretroviral agents (i.e., nucleoside analogues) has so far been documented to reduce viral load and increase CD4 lymphocytes in patients with CD4 cell counts below 500 cells/mm³.

The effects of indinavir (alone or combined with other antiretroviral agents) on the biological markers of disease activity, CD4 cell counts and serum viral RNA, were evaluated in several studies involving HIV-1 seropositive patients with CD4 cell counts <500 cells/mm³. These studies have documented that indinavir, 2.4 g/day was consistently associated with increases in median CD4 cell counts of 90-100 cells/mm³ and median declines in serum viral RNA in excess of 1 log₁₀ copies/ml which were sustained to at least 24 weeks. Approximately 40% of these patients had serum viral RNA levels decrease to below 500 copies/ml, the limit of detection of the assay.

In one study at 24 weeks, the median declines in serum viral RNA for the group treated with indinavir alone, the group treated with indinavir in combination with zidovudine and lamivudine, and the group treated with zidovudine plus lamivudine were 0.67 log₁₀ (89%), 1.88 log₁₀ (98%), and 0.66 log₁₀ (78%), respectively. At 24 weeks, the percentage of patients whose serum viral RNA levels had decreased to below the limit of detection of the assay (<500 copies/ml) were 35% and 91%, for the groups treated with indinavir alone or in combination, respectively. A total of 0% of the patients in the zidovudine plus
lamivudine group experienced this level of serum viral RNA decline at the 24 week time point. Median CD4 cell counts at 24 weeks were increased for all treatment groups.

5.2 Pharmacokinetic properties

Absorption
Indinavir is rapidly absorbed in the fasted state with a time to peak plasma concentration of 0.8 hours ± 0.3 hours (mean ± S.D.). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-800 mg dose range. Between 800-mg and 1000-mg dose levels, the deviation from dose-proportionality is less pronounced. As a result of the short half-life, 1.8 ± 0.4 hours, only a minimal increase in plasma concentrations occurred after multiple dosing.

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 86% reduction in C_{max}. Administration with light meals (e.g., dry toast with jam or fruit conserve, apple juice, and coffee with skimmed or fat-free milk and sugar or corn flakes, skimmed or fat-free milk and sugar) resulted in plasma concentrations comparable to the corresponding fasted values.

Distribution
Indinavir was not highly bound to human plasma proteins (39% unbound).

There are no data concerning the penetration of indinavir into the central nervous system in humans.

Biotransformation
Seven major metabolites were identified and the metabolic pathways were identified as glucuronidation at the pyridine nitrogen, pyridine-N-oxidation with and without 3'-hydroxylation on the indane ring, 3'-hydroxylation of indane, p-hydroxylation of phenylmethyl moiety, and N-depyridomethylation with and without the 3'-hydroxylation. *In vitro* studies with human liver microsomes indicated that 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 had little protease inhibitory activity.

Elimination
Over the 200-1000 mg dose range administered in both volunteers and HIV infected patients, there was a slightly greater than dose-proportional increase in urinary recovery of indinavir. Renal clearance (116 ml/min) of indinavir is concentration-independent over the clinical dose range. Less than 20% of indinavir is excreted renally. Mean urinary excretion of unchanged drug 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
Pharmacokinetics of indinavir do not appear to be affected by gender or by race.

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 400-mg dose. The mean half-life of indinavir increased to approximately 2.8 hours.

At steady state following a dosage regimen of 800 mg every 8 hours, HIV-seropositive patients in one study achieved AUC values of 28,713 nM-h, peak plasma concentrations of 11,144 nM and plasma concentrations at 8 hours post dose of 211 nM.
5.3 Preclinical Safety Data

Crystals have been seen in the urine of rats, one monkey, and one dog. The crystals have not been associated with drug-induced renal injury. 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 $\geq 160$ mg/kg/day. An increase in hepatic weight occurred in rats treated with indinavir at doses $\geq 40$ mg/kg/day and was accompanied by hepatocellular hypertrophy at doses $\geq 320$ mg/kg/day.

The maximum non-lethal oral dose of indinavir was at least 5000 mg/kg in rats and mice, the highest dose tested in acute toxicity studies.

Studies in rats indicated that uptake into brain tissue was limited, distribution into and out of the lymphatic system was rapid, and excretion into the milk of lactating rats was extensive. Distribution of indinavir across the placental barrier was significant in rats, but limited in rabbits.

Mutagenicity: Indinavir did not have any mutagenic or genotoxic activity in studies with or without metabolic activation.

Carcinogenicity: Carcinogenicity studies of indinavir are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains the excipients anhydrous lactose and magnesium stearate. The capsule shell contains the excipients gelatine, titanium dioxide, silicon dioxide, and sodium lauryl sulphate. The 400-mg capsules are printed with printing ink containing titanium dioxide (E 171), indigo carmine (E 132) and iron oxide (E 172).

The capsules are white opaque and coded CRIXIVAN™ 400 mg in green.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The shelf-life is 12 months.

6.4 Special precautions for storage

Sensitive to moisture. Store in a well-closed container.

6.5 Nature and contents of container

CRIXIVAN 400 mg is supplied in HDPE bottles with a polypropylene cap and a foil induction cap containing 90 or 180 capsules.

The containers contain desiccant canisters that should remain in the bottle. Patients should be advised not to swallow desiccant.
7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II
HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S)
RESPONSIBLE FOR BATCH RELEASE AND CONDITIONS
OF THE MARKETING AUTHORISATION
A. HOLDERS OF THE MANUFACTURING AUTHORISATIONS

Manufacturer of the finished medicinal product and responsible for importation and batch release in the European Economic Area:

Merck Sharp & Dohme B.V., Waarderweg 39, P.O. Box 581, 2003 PC Haarlem, The Netherlands

A Manufacturing Authorisation was issued on 13 February 1996 by the Ministry of Health, Welfare and Sports, P.O Box 5850, 5850 HW Rijswijk, The Netherlands.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non-renewable restricted medical prescription.

C. SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDER

The applicant, after having been consulted agreed to submit to the EMEA, within the defined time-frame, the information requested by the CPMP (letter dated 19 June 1996).


1. Re-assessment

Regular status reports from studies 033 (indinavir versus zidovudine versus indinavir/zidovudine), 037 (indinavir versus stavudine versus indinavir/stavudine) and 039 (indinavir versus zidovudine/lamivudine versus zidovudine/lamivudine/indinavir), should be reported every 6 months after CPMP opinion and final study reports should be submitted as soon as possible and the latest by 31 December 1997.
For the clinical end-point studies, 028 (indinavir versus zidovudine versus indinavir/zidovudine) and ACTG320 (zidovudine/lamivudine versus zidovudine/lamivudine/indinavir), results should be submitted the latest by 30 June 1998. Regular status reports of these studies should be submitted every six months. Results from the planned interim analysis (028) should be submitted as soon as it is available.

2. Other obligations

1. Only capsules from Capsugel should be used. If capsules from Shionogi are going to be used, they should conform to the same specifications.

2. The applicant should develop a specific analysis method for Compound I in Crixivan capsules by 31 October 1996 and reassess the shelf-life specifications for degradants when two full years production data have been collected.

3. The heavy metals test (Ph.Eur.) which utilise hydrogen sulphide instead of thioacetamide at the sulphate source should be described in detail and validated at the latest by 31 October 1996.

4. Full time stability data on production batches of the finished product should be submitted at the latest by 31 December 1997.

5. An identification test for the plastic material should be included in the routine specifications for the closures by 31 October 1996.

6. The results from controlled clinical trials studying interactions with the following products should be provided when finalised and not later than the time-frame as specified below for each medicinal product:

   - methadone (by 31 July 1997)
   - rifampicin (by 30 November 1996)
   - dose recommendations during concomitant rifabutin treatment should be substantiated (by 31 December 1997)
   - dose recommendations during concomitant ketoconazole treatment should be substantiated (by 31 July 1997)
   - food (by 30 September 1997)

7. The Company is invited to present no later than the time-frame as specified below, a development plan for paediatric patients and agrees to inform the EMEA on the outcome of these investigations:

   • Results from the ongoing efficacy study with the capsules formulation in children (>3 years - 18 years) based on surrogate markers, by 30 June 1997.

   • Results on the feasibility of a liquid formulation and pharmacokinetic information from adults using this liquid formulation by 30 September 1997. Based on these results, a decision for conducting further studies in children should be made.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
180 Capsules

**CRIXIVAN 200 mg**

**Indinavir**

1 capsule contains:
Indinavir sulphate equivalent to indinavir 200 mg, anhydrous lactose, colorants [titanium dioxide (E 171) and indigo carmine (E 132)] and other constituents.

Capsules should be swallowed whole.
Sensitive to moisture, keep the container tightly closed and protected from humidity.
Desiccant should not be removed from the container.
Desiccant should not be swallowed.
Keep the medicine out of reach of children.
Consult attached leaflet before use.
Medical product subject to medical prescription.

Batch No:
Expiry date: Mo/Year

**Marketing Authorisation Holder :**
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Marketing authorisation number:
270 Capsules

**CRIXIVAN 200 mg**

Indinavir

1 capsule contains:
Indinavir sulphate equivalent to indinavir 200 mg, anhydrous lactose, colorants [titanium dioxide (E 171) and indigo carmine (E 132)] and other constituents.

Capsules should be swallowed whole.
Sensitive to moisture, keep the container tightly closed and protected from humidity.
Desiccant should not be removed from the container.
Desiccant should not be swallowed.
Keep the medicine out of reach of children.
Consult attached leaflet before use.
Medical product subject to medical prescription.

Batch No:
Expiry date: Mo/Year

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Marketing authorisation number:
360 Capsules

**CRIXIVAN 200 mg**

Indinavir

1 capsule contains:
Indinavir sulphate equivalent to indinavir 200 mg, anhydrous lactose, colorants [titanium dioxide (E 171) and indigo carmine (E 132)] and other constituents.

Capsules should be swallowed whole.
Sensitive to moisture, keep the container tightly closed and protected from humidity.
Desiccant should not be removed from the container.
Desiccant should not be swallowed.
Keep the medicine out of reach of children.
Consult attached leaflet before use.
Medical product subject to medical prescription.

Batch No:
Expiry date: Mo/Year

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Marketing authorisation number:
90 Capsules

**CRIXIVAN 400 mg**

Indinavir

1 capsule contains:
Indinavir sulphate equivalent to indinavir 400 mg, anhydrous lactose, colorants [titanium dioxide (E 171), iron oxide (E 172) and indigo carmine (E 132)] and other constituents.

Capsules should be swallowed whole.
Sensitive to moisture, keep the container tightly closed and protected from humidity.
Desiccant should not be removed from the container.
Desiccant should not be swallowed.
Keep the medicine out of reach of children.
Consult attached leaflet before use.
Medical product subject to medical prescription.

Batch No:
Expiry date: Mo/Year

Marketing Authorisation Holder :
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Marketing authorisation number:
180 Capsules

**CRIXIVAN 400 mg**

Indinavir

1 capsule contains:
Indinavir sulphate equivalent to indinavir 400 mg, anhydrous lactose, colorants [titanium dioxide (E 171), iron oxide (E 172) and indigo carmine (E 132)] and other constituents.

Capsules should be swallowed whole.
Sensitive to moisture, keep the container tightly closed and protected from humidity.
Desiccant should not be removed from the container.
Desiccant should not be swallowed.
Keep the medicine out of reach of children.
Consult attached leaflet before use.
Medical product subject to medical prescription.

Batch No:
Expiry date: Mo/Year

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Marketing authorisation number:
B. PACKAGE LEAFLET
Please read this leaflet carefully before you start to take your medicine, even if you have read a leaflet for CRIXIVAN before. Some of the information in the previous leaflet may have changed. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

What is CRIXIVAN?

CRIXIVAN 200 mg capsules contain 250 mg of indinavir sulphate corresponding to 200 mg of indinavir.

In addition, CRIXIVAN contains the following excipients: anhydrous lactose, magnesium stearate, gelatine, silicon dioxide, sodium lauryl sulphate and titanium dioxide (E 171). CRIXIVAN is available as a 200 mg capsule. The capsules are printed with printing ink containing titanium dioxide (E 171) and indigo carmine (E 132).

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 number of HIV particles in blood.

Why has my doctor prescribed CRIXIVAN?

Your doctor has prescribed CRIXIVAN for you because you have HIV infection.

Complete information on the clinical effects of CRIXIVAN is not yet available but further studies are in progress.

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

You should know that CRIXIVAN is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. You should, therefore, remain under the care of your doctor while taking CRIXIVAN.

Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

CRIXIVAN has been shown to greatly lower the number of HIV particles in the blood. The clinical benefits of this effect are presently being studied.

When should CRIXIVAN not be taken?

Do not take CRIXIVAN if you experience a severe allergic reaction to any component of the drug.
What should I inform my doctor of before I take CRIXIVAN?

Inform your doctor about any past or present medical problems, including liver disease due to cirrhosis, or allergies.

Inform your doctor if you have kidney problems.

Because it is important to drink large amounts of liquids while taking CRIXIVAN, please inform your doctor if you have fluid intake restrictions.

**Use in pregnancy and breast-feeding.**

It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman. If you are pregnant, you should take CRIXIVAN only if your doctor decides it is clearly needed.

Inform your doctor if you are pregnant or intend to become pregnant.

Inform your doctor if you are breast-feeding.

**Use in children.**

Should not be used in children.

**Can I take CRIXIVAN with other medicines?**

CRIXIVAN may be taken with a number of medications that are commonly used in HIV infection. These include zidovudine, didanosine, lamivudine, stavudine, quinidine, cimetidine, clarithromycin, isoniazid, fluconazole and trimethoprim/sulfamethoxazole. No studies have been done with CRIXIVAN taken with other drugs of this class (protease inhibitors). However, there are some medications that may not be taken with CRIXIVAN or that require dosage reduction of that medicine or CRIXIVAN. Drugs that cannot be taken with CRIXIVAN include rifampicin, terfenadine, astemizole, cisapride, alprazolam, triazolam and midazolam. Drugs that require dosage reduction of that medicine or CRIXIVAN include rifabutin and ketoconazole. Also consult your doctor if you are taking itraconazole, phenobarbital, phenytoin, dexamethasone, carbamazepine, ritonavir, methadone or any other medications.

You should always inform your doctor about all drugs you are taking or plan to take, including those obtained without a prescription.

**Can I drive or operate machinery while I am taking CRIXIVAN?**

There is no specific information to suggest that CRIXIVAN affects your ability to drive and use machinery. However, dizziness and blurred vision have been reported during treatment with CRIXIVAN. If you experience these you should avoid driving or operating machinery.

**How should CRIXIVAN be taken?**

CRIXIVAN is in capsule form and must be taken by mouth. The usual dose is 800 mg given as four 200 mg capsules at regular eight hour intervals. CRIXIVAN must be taken at intervals of 8 hours for full effectiveness.

CRIXIVAN should be swallowed whole.

CRIXIVAN should be taken without food but with water 1 hour before or 2 hours after a meal. If water is not preferred, CRIXIVAN can be taken with skimmed or low-fat milk, juice, coffee, or tea. If CRIXIVAN cannot be taken without food, a low-fat light meal, such as dry toast with jam or fruit conserve, juice and
coffee with skimmed or low-fat milk, and sugar or a light meal such as corn flakes with skimmed or low-fat milk and sugar is acceptable. At any other time you can eat whatever you like.

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.

CRIXIVAN has caused kidney stones in some patients. Therefore, it is important to drink at least 1.5 liters (~ 48 ounces) of liquids during each day while taking CRIXIVAN to help reduce the risk of forming kidney stones.

It is important that you take CRIXIVAN exactly as your doctor prescribes and that you do not stop taking it without first consulting your doctor.

**What should I do if I miss a dose?**

Take CRIXIVAN 3 times a day at regular 8-hour intervals. However if you miss a dose, do not take it later in the day. Simply continue to follow your usual schedule.

**What undesirable effects may CRIXIVAN have?**

Any drug may have unintended or undesirable effects, so-called side effects. CRIXIVAN has been shown to be generally well tolerated. Side effects include sudden severe back pain, caused by kidney stones, with or without blood in the urine; weakness/fatigue; abdominal pain; diarrhea; dyspepsia; nausea; dizziness; headache; dry skin; rash; taste perversion; vomiting; flatulence; insomnia; decreased or abnormal skin sensation; and muscle pain.

Other side effects may occur with CRIXIVAN. Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects. Inform your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

Inform your doctor if you are intolerant to lactose. Each capsule contains 74 mg lactose (anhydrous). This quantity is probably not sufficient to induce specific symptoms of intolerance.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

**How can I learn more about CRIXIVAN?**

Not all the information about the drug is printed here. If you have any additional questions, ask your doctor or pharmacist who have more detailed information about CRIXIVAN and HIV infection.

**How long should I keep my medicine?**

Do not use this medicine after the month and year shown by the four numbers following expiry date on the container. The first two numbers indicate the month; the last two numbers indicate the year.
How should I store CRIXIVAN?

CRIXIVAN capsules are sensitive to moisture. Store CRIXIVAN in the original container, tightly closed and protected from humidity. Do not remove desiccant canister from the bottle. Do not swallow the desiccant.

Keep CRIXIVAN safely away from children.

This package leaflet was last revised___________.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België**
Chaussée de Waterloo/Waterloosesteenweg 1135
1180 Bruxelles/Brussel
Tel. 02/373 42 11

**Luxembourg**
Chaussée de Waterloo 1135
1180 Bruxelles
Belgique
Tel. 02/373 42 11

**Danmark**
Smedeland 8
2600 Glostrup
Tlf. 43 28 77 66

**Nederland**
Postbus 581
2003 PC Haarlem
Tel. 023/5153153

**Deutschland**
Lindenplatz 1
D-85540 Haar
Tel. 089/45611 0

**Österreich**
Gunoldstr. 14
A-1190 Wien
Tel. 0222/36 15 50 0

**España**
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Tel. 91/321 06 00

**Portugal**
Rua Consiglieri Pedroso, 121-123
2745 Queluz de Baixo
Tel. 01/4347000

**Suomi**
PL. 98
02231 ESPOO
Puh. 90/804650

**France**
3, Avenue Hoche
75114 Paris Cedex 08
Tel. 1 47 54 87 00

**Sverige**
Box 7125
192 07 Sollentuna
Tel. 08/626 1400

**Ireland**
Hertford Road
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Hertfordshire EN11 9BU
UK
Tel. 01992/467272

**United Kingdom**
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
UK
Tel. 01992/467272

**Italia**
via G. Fabbroni, 6
00191 ROMA
Tel. 06/361911
Please read this leaflet carefully before you start to take your medicine, even if you have read a leaflet for CRIXIVAN before. Some of the information in the previous leaflet may have changed. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

What is CRIXIVAN?

CRIXIVAN 400 mg capsules contain 500 mg of indinavir sulphate corresponding to 400 mg of indinavir.

In addition, CRIXIVAN contains the following excipients: anhydrous lactose, magnesium stearate, gelatine, silicon dioxide, sodium lauryl sulphate and titanium dioxide (E 171). CRIXIVAN is available as a 400 mg capsule. The capsules are printed with printing ink containing titanium dioxide (E 171), indigo carmine (E 132) and iron oxide (E 172).

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 number of HIV particles in blood.

Marketing Authorisation Holder
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

Product Manufacturer
Merck Sharp & Dohme B.V.
Waarderweg 39
P.O. Box 581
2003 PC Haarlem
the Netherlands

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

You should know that CRIXIVAN is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. You should, therefore, remain under the care of your doctor while taking CRIXIVAN.

Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

CRIXIVAN has been shown to greatly lower the number of HIV particles in the blood. The clinical benefits of this effect are presently being studied.

When should CRIXIVAN not be taken?

Do not take CRIXIVAN if you experience a severe allergic reaction to any component of the drug.
What should I inform my doctor of before I take CRIXIVAN?

Inform your doctor about any past or present medical problems, including liver disease due to cirrhosis, or allergies.

Inform your doctor if you have kidney problems.

Because it is important to drink large amounts of liquids while taking CRIXIVAN, please inform your doctor if you have fluid intake restrictions.

Use in pregnancy and breast-feeding.

It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman. If you are pregnant, you should take CRIXIVAN only if your doctor decides it is clearly needed.

Inform your doctor if you are pregnant or intend to become pregnant.

Inform your doctor if you are breast-feeding.

Use in children.

Should not be used in children.

Can I take CRIXIVAN with other medicines?

CRIXIVAN may be taken with a number of medications that are commonly used in HIV infection. These include zidovudine, didanosine, lamivudine, stavudine, quinidine, cimetidine, clarithromycin, isoniazid, fluconazole and trimethoprim/sulfamethoxazole. No studies have been done with CRIXIVAN taken with other drugs of this class (protease inhibitors). However, there are some medications that may not be taken with CRIXIVAN or that require dosage reduction of that medicine or CRIXIVAN. Drugs that cannot be taken with CRIXIVAN include rifampicin, terfenadine, astemizole, cisapride, alprazolam, triazolam and midazolam. Drugs that require dosage reduction of that medicine or CRIXIVAN include rifabutin and ketoconazole. Also consult your doctor if you are taking itraconazole, phenobarbital, phenytoin, dexamethasone, carbamazepine, ritonavir, methadone or any other medications.

You should always inform your doctor about all drugs you are taking or plan to take, including those obtained without a prescription.

Can I drive or operate machinery while I am taking CRIXIVAN?

There is no specific information to suggest that CRIXIVAN affects your ability to drive and use machinery. However, dizziness and blurred vision have been reported during treatment with CRIXIVAN. If you experience these you should avoid driving or operating machinery.

How should CRIXIVAN be taken?

CRIXIVAN is in capsule form and must be taken by mouth. The usual dose is 800 mg given as two 400 mg capsules at regular eight hour intervals. CRIXIVAN must be taken at intervals of 8 hours for full effectiveness.

CRIXIVAN should be swallowed whole.

CRIXIVAN should be taken without food but with water 1 hour before or 2 hours after a meal. If water is not preferred, CRIXIVAN can be taken with skimmed or low-fat milk, juice, coffee, or tea. If CRIXIVAN cannot be taken without food, a low-fat light meal, such as dry toast with jam or fruit conserve, juice and...
coffee with skimmed or low-fat milk, and sugar or a light meal such as corn flakes with skimmed or low-fat milk and sugar is acceptable. At any other time you can eat whatever you like.

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.

CRIXIVAN has caused kidney stones in some patients. Therefore, it is important to drink at least 1.5 liters (~ 48 ounces) of liquids during each day while taking CRIXIVAN to help reduce the risk of forming kidney stones.

It is important that you take CRIXIVAN exactly as your doctor prescribes and that you do not stop taking it without first consulting your doctor.

**What should I do if I miss a dose?**

Take CRIXIVAN 3 times a day at regular 8-hour intervals. However if you miss a dose, do not take it later in the day. Simply continue to follow your usual schedule.

**What undesirable effects may CRIXIVAN have?**

Any drug may have unintended or undesirable effects, so-called side effects. CRIXIVAN has been shown to be generally well tolerated. Side effects include sudden severe back pain, caused by kidney stones, with or without blood in the urine; weakness/fatigue; abdominal pain; diarrhoea; dyspepsia; nausea; dizziness; headache; dry skin; rash; taste perversion; vomiting; flatulence; insomnia; decreased or abnormal skin sensation; and muscle pain.

Other side effects may occur with CRIXIVAN. Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects. Inform your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

Inform your doctor if you are intolerant to lactose. Each capsule contains 149 mg lactose (anhydrous). This quantity is probably not sufficient to induce specific symptoms of intolerance.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

**How can I learn more about CRIXIVAN?**

Not all the information about the drug is printed here. If you have any additional questions, ask your doctor or pharmacist who have more detailed information about CRIXIVAN and HIV infection.

**How long should I keep my medicine?**

Do not use this medicine after the month and year shown by the four numbers following expiry date on the container. The first two numbers indicate the month; the last two numbers indicate the year.
**How should I store CRIXIVAN?**

CRIXIVAN capsules are sensitive to moisture. Store CRIXIVAN in the original container, tightly closed and protected from humidity. Do not remove desiccant canister from the bottle. Do not swallow the desiccant.

Keep CRIXIVAN safely away from children.

This package leaflet was last revised______________.
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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