ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains indinavir sulphate corresponding to 200 mg of indinavir.

Excipient with known effect
Each 200 mg capsule contains 74.8 mg lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule.

The capsules are semi–translucent white and coded 'CRIXIVAN ™ 200 mg' in blue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRIXIVAN is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV–1 infected adults.

4.2 Posology and method of administration

CRIXIVAN should be administered by physicians who are experienced in the treatment of HIV infection. On the basis of current pharmacodynamic data, indinavir must be used in combination with other antiretroviral agents. When indinavir is administered as monotherapy resistant viruses rapidly emerge (see section 5.1).

Posology
The recommended dose of indinavir is 800 mg orally every 8 hours.

Data from published studies suggest that CRIXIVAN 400 mg in combination with ritonavir 100 mg, both administered orally twice daily, may be an alternative dosing regimen. The suggestion is based on limited published data (see section 5.2).

A dose reduction of indinavir to 600 mg every 8 hours should be considered when administering itraconazole or ketoconazole concurrently (see section 4.5).

Special populations
Hepatic impairment
In patients with mild–to–moderate hepatic impairment due to cirrhosis, the dose of indinavir should be reduced to 600 mg every 8 hours. The recommendation is based on limited pharmacokinetic data (see section 5.2). Patients with severe hepatic impairment have not been studied; therefore, no dosing recommendations can be made (see section 4.4).

Renal impairment
Safety in patients with impaired renal function has not been studied; however, less than 20 % of indinavir is excreted in the urine as unchanged medicinal product or metabolites (see section 4.4).

Paediatric population
The safety and efficacy of CRIXIVAN in children under the age of 4 years have not been established (see section 5.1 and 5.2). Currently available data in children above the age of 4 years are described in sections 4.8, 5.1, and 5.2.

Method of administration
The hard 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.

If co-administered with ritonavir, CRIXIVAN may be administered with or without food.

To ensure adequate hydration, it is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Indinavir with or without ritonavir should not be administered concurrently with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4. Inhibition of CYP3A4 by both CRIXIVAN and ritonavir could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see section 4.5).

CRIXIVAN with or without ritonavir should not be administered concurrently with amiodarone, terfenadine, cisapride, astemizole, quetiapine, alprazolam, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), pimozide, ergot derivatives, simvastatin or lovastatin (see section 4.4).

Combination of rifampicin with CRIXIVAN with or without concomitant low-dose ritonavir is contraindicated (see section 4.5). Concurrent use of indinavir with herbal preparations containing St John's wort (Hypericum perforatum) is contraindicated (see section 4.5).

In addition, indinavir with ritonavir must not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Indinavir must not be given with ritonavir to patients with decompensated liver disease as ritonavir is principally metabolized and eliminated by the liver (see section 4.4).

When CRIXIVAN is used with ritonavir, consult the Summary of Product Characteristics of ritonavir for additional contraindications.

4.4 Special warnings and precautions for use

Nephrolithiasis and tubulointerstitial nephritis
Nephrolithiasis has occurred with indinavir therapy in adult patients with a cumulative frequency of 12.4 % (range across individual trials: 4.7 % to 34.4 %). The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN; however, the risk over time remains relatively constant. In some cases, nephrolithiasis 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. for 1–3 days) during the acute episode of nephrolithiasis or discontinuation of therapy may be considered. Evaluation may consist of urinalysis, serum BUN and creatinine, and ultrasound of the bladder and kidneys. Adequate hydration is recommended in all patients on indinavir (see sections 4.2 and 4.8).

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

Cases of interstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leucocyturia (> 100 cells/high power field). In patients at increased risk, urinary screening should be considered. If persistent severe leucocyturia is found, further investigation might be warranted.

Medicinal products interactions
Indinavir should be used cautiously with other medicinal products that are potent inducers of CYP3A4. Co–administration may result in decreased plasma concentrations of indinavir and as a consequence an increased risk for suboptimal treatment and facilitation of development of resistance (see section 4.5).

If indinavir is given with ritonavir, the potential interaction may be increased. The Interactions section of the SPC for ritonavir should also be consulted for information about potential interactions.

Atazanavir as well as indinavir are associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UDP-glucuronosyltransferase (UGT). Combinations of atazanavir with or without ritonavir and Crixivan have not been studied and co-administration of these medicinal products is not recommended due to risk of worsening of these adverse reactions.

Concomitant use of indinavir with lovastatin or simvastatin is not recommended 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 must also be exercised if indinavir is used concurrently with atorvastatin. The interaction of indinavir or indinavir/ritonavir with pravastatin or fluvastatin is not known (see section 4.5).

Co–administration of CRIXIVAN with sildenafil, tadalafil and vardenafil (PDE5 inhibitors) are 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 section 4.5).

HIV Transmission
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 indinavir.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease
The safety and efficacy of indinavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

An increased incidence of nephrolithiasis has been observed in patients with underlying liver disorders when treated with indinavir.

Immune Reactivation Syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Patients with coexisting conditions
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with PIs. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with PIs was continued or re-introduced 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.

Patients with mild–to–moderate hepatic insufficiency due to cirrhosis will require a dose reduction of indinavir due to decreased metabolism of indinavir (see section 4.2). 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 medicinal product or metabolites (see section 4.2).

Osteonecrosis:
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lactose
This medicinal product contains 299.2 mg of lactose in each 800 mg dose (maximum single dose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of indinavir is mediated by the cytochrome P450 enzyme CYP3A4. Therefore, other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of indinavir. Similarly, indinavir might also modify the pharmacokinetics of other substances that share this metabolic pathway. Boosted indinavir (indinavir with ritonavir) may have additive pharmacokinetic effects on substances that share the CYP3A4 pathway as both ritonavir and indinavir inhibit the cytochrome P450 enzyme CYP3A4.

Indinavir with or without ritonavir should not be administered concurrently with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4. Inhibition of CYP3A4 by both CRIXIVAN and ritonavir could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions. CRIXIVAN with or without ritonavir should not be administered concurrently with amiodarone, terfenadine, cisapride, astemizole, quetiapine, alprazolam, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see Table 1 and 2 below), pimozide, ergot derivatives, simvastatin or lovastatin. In addition, indinavir with ritonavir should not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Concurrent use of indinavir with rifampicin or herbal preparations containing St John's wort (Hypericum perforatum) is contraindicated.

Medicinal products listed above are not repeated in Table 1 and 2 unless specific interaction data is available.

Refer also to sections 4.2 and 4.3.

Table 1. Interactions and dose recommendations with other medical products – <u>UNBOOSTED INDINAVIR</u>

Interactions between indinavir and other medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change (≤ +/- 20 %) as "↔", single dose as "SD", once daily as "QD", twice daily as "BID", three times daily as "TID", and four times daily as "QID").

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Didanosine Formulation with buffer	No formal interaction study has been performed. 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. Antiretroviral activity was unaltered when didanosine was administered 3 hours after treatment with indinavir.	Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach.
Didanosine enteric-coated 400 mg SD (Indinavir 800 mg SD)	Indinavir: ↔ (Relative to Indinavir 800 mg SD alone) Didanosine: ↔	Can be administered without any restrictions with respect to time of administration or food.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Stavudine 40 mg BID (Indinavir 800 mg TID)	Indinavir AUC: ↔ Indinavir C_{min} :↔ (Relative to Indinavir 800 mg TID alone) Stavudine AUC: ↑ 21 % Stavudine C_{min}: not evaluated	Indinavir and NRTIs can be co-administered without dose adjustment.
Zidovudine 200 mg TID (Indinavir 1,000 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↔ (Relative to Indinavir 1,000 mg TID alone) Zidovudine AUC: ↔ Zidovudine C_{min}: ↑ 51 %	
Zidovudine/Lamivudine 200/150 mg TID (Indinavir 800 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↔ (Relative to Indinavir 800 mg TID alone) Zidovudine AUC: ↑ 39 % Zidovudine C_{min}: ↔ Lamivudine AUC: ↔ Lamivudine C_{min}: ↔	
NNRTIs		
Delavirdine 400 mg TID (Indinavir 600 mg TID) Delavirdine 400 mg TID Indinavir 400 mg TID	Indinavir AUC: ↑ 53 % Indinavir C_{min} ↑ 298 % (Relative to Indinavir 800 mg TID alone) Indinavir AUC: ↔ Indinavir C_{min}: ↑ 118 % (Relative to Indinavir 800 mg TID alone) Delavirdine: ↔	Dose reduction of CRIXIVAN to 400-600 mg every 8 hours should be considered.
Efavirenz 600 mg QD (Indinavir 1,000 mg TID) Efavirenz 200 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↓ 46 % Indinavir C_{min}: ↓ 57 % (Relative to Indinavir 800 mg TID alone) An increased dose (1,000 mg TID) of indinavir does not compensate for the inducing effect of efavirenz. Indinavir AUC: ↓ 31 % Indinavir C_{min}: ↓ 40 % Efavirenz AUC: ↔	No specific dose recommendation can be given.
Nevirapine 200 mg BID (Indinavir 800 mg TID)	Indinavir AUC: ↓ 28 % Nevirapine: ↔ (CYP3A induction)	A dose increase of indinavir to 1,000 mg every 8 hours should be considered if given with nevirapine.
PIs		
Amprenavir 1,200 mg BID (Indinavir 1,200 mg BID)	Amprenavir AUC: ↑ 90 % Indinavir: ↔	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Atazanavir	Interaction not studied	Combination of atazanavir with or without ritonavir and Crixivan are not recommended due to increased risk of hyperbilirubinemia (see section 4.4).
Ritonavir 100 mg BID (Indinavir 800 mg BID)	Indinavir AUC_{24hr}:↑ 178 % Indinavir C_{min}:↑11-fold; (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC: ↑ 72 % Ritonavir C_{min}: ↑ 62 %	The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Preliminary clinical data suggest that CRIXIVAN 400 mg in combination with ritonavir 100 mg, both administered orally twice daily, may be an alternative dosing regimen (see section 5.2). A boosted dose of 800 mg indinavir/100 mg ritonavir twice daily results in increased risk of adverse events.
Ritonavir 200 mg BID (Indinavir 800 mg BID)	Indinavir AUC_{24hr}:↑266 % Indinavir C_{min}:↑24-fold; (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC: ↑ 96 % Ritonavir C_{min}: ↑ 371 %	
Ritonavir 400 mg BID (Indinavir 800 mg BID)	Indinavir AUC_{24hr}:↑220 % Indinavir C_{min}:↑ 24-fold (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC_{24hr}: ↔	
Ritonavir 400 mg BID (Indinavir 400 mg BID)	Indinavir AUC_{24hr}:↑68 % Indinavir C_{min}: ↑ 10-fold (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC_{24hr}: ↔	
Ritonavir 100 mg BID (Indinavir 400 mg BID)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 800 mg TID alone*)	
	(*historical controls	

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Saquinavir 600 mg SD (hard gel capsule formulation) (Indinavir 800 mg TID)	Saquinavir AUC: ↑ 500 % Saquinavir C_{min}: ↑ 190 % (Relative to saquinavir 600 mg SD (hard gel formulation) alone)	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Saquinavir 800 mg SD (soft gel capsule formulation) (Indinavir 800 mg TID)	Saquinavir AUC: ↑ 620 % Saquinavir C_{min}: ↑ 450 % (Relative to saquinavir 800 mg SD (soft gel formulation) alone)	
Saquinavir 1,200 mg SD (soft gel capsule formulation) (Indinavir 800 mg TID)	Saquinavir AUC: ↑ 360 % Saquinavir C_{min}: ↑ 450 % (Relative to saquinavir 1,200 mg (soft gel formulation) alone) The design of the study does not allow for definitive evaluation of the effect of saquinavir on indinavir, but suggests there is less than a two–fold increase in indinavir AUC_{8h} during co–administration with saquinavir	
Antibiotics		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg BID (Indinavir 400 mg QID)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg QID alone) Sulphamethoxazole AUC and C_{min}: ↔	Indinavir and sulphamethoxazole/ trimethoprim can be co-administered without dose adjustment.
Antifungals		
Fluconazole 400 mg QD (Indinavir 1,000 mg TID)	Indinavir AUC: ↓ 24 % Indinavir C_{min}: ↔ (Relative to Indinavir 1,000 mg TID alone)	Indinavir and fluconazole can be co-administered without dose adjustment.
Itraconazole 200 mg BID (Indinavir 600 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↑ 49 % (Relative to Indinavir 800 mg TID alone)	Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended with administering itraconazole concurrently.
Ketoconazole 400 mg QD (Indinavir 600 mg TID) Ketoconazole 400 mg QD (Indinavir 400 mg TID)	Indinavir AUC: ↓ 20 % Indinavir C_{min}: ↑ 29 % (Relative to Indinavir 800 mg TID alone) Indinavir AUC ↓ 56 % Indinavir C_{min} ↓ 27 % (Relative to Indinavir 800 mg TID alone)	Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.
Anti-Mycobacterial		
Isoniazid 300 mg QD (Indinavir 800 mg TID)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 800 mg TID alone) Isoniazid AUC and C_{min}: ↔	Indinavir and isoniazid can be co-administered without dose adjustment.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Rifabutin 300 mg QD (Indinavir 800 mg TID) Rifabutin 150 mg QD (Indinavir 800 mg TID)	Indinavir AUC ↓ 34 % Indinavir C_{min} : ↓ 39 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC: ↑ 173 % Rifabutin C_{min}: ↑ 244 % (Relative to rifabutin 300 mg QD alone) Indinavir AUC: ↓ 32 % Indinavir C_{min}: ↓ 40 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC*: ↑ 54 % Rifabutin C_{min*}: ↑ 99 % (*Relative to rifabutin 300 mg QD alone. No data has been obtained comparing rifabutin 150 mg QD in combination with indinavir 800 mg TID with a reference dose of 150 mg rifabutin alone)	Dose reduction of rifabutin and dose increase of Crixivan has not been confirmed in clinical studies. Therefore co-administration is not recommended. If rifabutin treatment is required, alternative agents for treating HIV infection should be sought.
Rifampicin 600 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↓ 92 % (Relative to Indinavir 800 mg TID alone) This effect is due to an induction of CYP3A4 by rifampicin.	The use of rifampicin with indinavir is contraindicated.
ANALGESICS		
Methadone 20-60 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↔ (Relative to Indinavir 800 mg TID historical controls) Methadone AUC and C_{min}: ↔	Indinavir and methadone can be co-administered without dose adjustment.
ANTIARRHYTHMICS		
Quinidine 200 mg SD (Indinavir 400 mg SD)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg SD) ↑ Quinidine concentration expected (CYP3A4 inhibition by indinavir)	Caution is warranted and therapeutic concentration monitoring is recommended for quinidine when coadministered with CRIXIVAN. The use of indinavir/ritonavir with quinidine is contraindicated.
ANTIASTHMATIC		
Theophylline 250 mg SD (Indinavir 800 mg TID)	Theophylline AUC and C_{min}: ↔	Indinavir and theophylline can be co-administered without dose adjustment.
ANTICOAGULANT		
Warfarin	Not studied, combined administration may result in increased warfarin levels.	Dose adjustment of warfarin may be required.
ANTICONVULSANTS		
Carbamazepine, phenobarbital phenytoin	Indinavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of these anticonvulsants. Concomitant use of medicinal products that are inducers of CYP3A4, such as carbamazepine, phenobarbital and phenytoin may reduce indinavir plasma concentrations.	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with indinavir.
ANTIDEPRESSANTS		
Venlafaxine 50 mg TID (Indinavir 800 mg SD)	Indinavir AUC: ↓ 28 % (Relative to Indinavir 800 mg SD alone) Venlafaxine and active metabolite O-desmethyl-venlafaxine: ↔	The clinical significance of this finding is unknown.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTIPSYCHOTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by indinavir, concentrations of quetiapine are expected to increase.	Concomitant administration of indinavir and quetiapine may increase plasma concentrations of quetiapine leading to quetiapine-related toxicity, including coma. Co-administration of quetiapine with indinavir is contraindicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS		
Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blocker concentration Calcium channel blockers are metabolized by CYP3A4 which is inhibited by indinavir.	Caution is warranted and clinical monitoring of patients is recommended.
HERBAL MEDICATIONS		
St. John's wort (Hypericum perforatum) 300 mg TID (Indinavir 800 mg TID)	Indinavir AUC: ↓ 54 % Indinavir C_{min}: ↓ 81 % (Relative to Indinavir 800 mg TID alone) Reduction in indinavir concentrations due to induction of medicinal product metabolising and/or transport proteins by St. John's wort.	Herbal preparations containing St. John's wort are contraindicated with Crixivan. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible indinavir levels. Indinavir levels may increase on stopping St. John's wort, and the dose of CRIXIVAN may need adjusting. The inducing effect may persist up to 2 weeks after cessation of treatment with St. John's wort.
HISTAMINE H_2 ANTAGONIST		
Cimetidine 600 mg BID (Indinavir 400 mg SD)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg SD alone)	Indinavir and cimetidine can be co-administered without dose adjustment.
HMG-CoA REDUCTASE INHIBITORS		
Lovastatin, simvastatin	Indinavir inhibits CYP3A4 and as a result is expected to markedly increase the plasma concentrations of these HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism.	Combination contraindicated due to an increased risk of myopathy including rhabdomyolysis.
Rosuvastatin	Interaction not studied. Interaction study with Lopinavir/ritonavir + rosuvastatin: Rosuvastatin AUC ↑ 2.08-fold Rosuvastatin Cmax ↑ 4.66-fold (Mechanism unknown)	Combination not recommended
Atorvastatin	↑ atorvastatin concentration Atorvastatin is less dependent on CYP3A4 for metabolism than lovastatin or simvastatin	Use the lowest possible dose of atorvastatin with careful monitoring. Caution is advised.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Pravastatin, fluvastatin	Interaction not studied Metabolism of pravastatin and fluvastatin is not dependent on CYP3A4. Interaction via effects on transport proteins cannot be excluded.	Interaction unknown. If no alternative treatment is available, use with careful monitoring.
IMMUNOSUPPRESSIVES		
Cyclosporine A	Cyclosporine A (CsA) levels markedly increase in patients on PIs, including indinavir.	CsA levels require progressive dose adjustment using therapeutic medicinal product monitoring.
ORAL CONTRACEPTIVES		
Norethindrone/ethinyl estradiol 1/35 1 mcg QD (Indinavir 800 mg TID)	Norethindrone AUC: ↑ 26 % Norethindrone C_{min}: ↑ 44 %	Indinavir and norethindrone/ethinyl estradiol 1/35 can be co-administered without dose adjustment.
PDE5 INHIBITOR		
Sildenafil 25 mg SD (Indinavir 800 mg TID)	Indinavir AUC: ↑ 11 % Sildenafil AUC ↑ 340 % Coadministration of CRIXIVAN with sildenafil is likely to result in an increase of sildenafil by competitive inhibition of metabolism.	Sildenafil dose should not exceed a maximum of 25 mg in a 48-hour period in patients receiving concomitant indinavir therapy.
Vardenafil 10 mg SD (Indinavir 800 mg TID)	Vardenafil AUC: ↑ 16-fold Coadministration of CRIXIVAN with vardenafil is likely to result in an increase of vardenafil by competitive inhibition of metabolism.	Vardenafil dose should not exceed a maximum of 2.5 mg in a 24-hour period in patients receiving concomitant indinavir therapy.
Tadalafil	Interaction not studied Coadministration of CRIXIVAN with tadalafil is likely to result in an increase of tadalafil by competitive inhibition of metabolism.	Tadalafil dose should not exceed a maximum of 10 mg in a 72 hour period in patients receiving concomitant indinavir therapy.
SEDATIVES/HYPNOTICS		
Midazolam (parenteral)	Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally. Midazolam is extensively metabolized by CYP3A4.	CRIXIVAN and oral midazolam should not be coadministered (see section 4.3). Caution should be used with coadministration of CRIXIVAN and parenteral midazolam. If CRIXIVAN is coadministered with parenteral midazolam, it should be done in an intensive care unit with close clinical monitoring in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
STEROIDS		
Dexamethasone	Interaction not studied ↑ dexamethasone exposure expected (CYP3A inhibition). ↓ indinavir plasma concentrations may be expected (CYP3A induction).	Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with indinavir.

Table 2. Interactions and dose recommendations with other medical products – <u>INDINAVIR BOOSTED WITH RITONAVIR.</u> *No specific interaction studies have been performed with the boosted dose 400 mg indinavir with 100 mg ritonavir.*

Interactions between indinavir/ritonavir and other medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change (≤ +/- 20 %) as "↔", single dose as "SD", once daily as "QD", twice daily as "BID", three times daily as "TID", and four times daily as "QID").

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
Amprenavir	Amprenavir 1,200 mg BID AUC ↑90 % with 800 mg TID indinavir alone (see Table 1). Amprenavir 600 mg BID AUC ↑ 64 % with 100 mg BID ritonavir alone (relative to amprenavir 1,200 mg BID alone). Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. There are no interaction data available on the coadministration of indinavir/ritonavir and amprenavir.	The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Ritonavir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations.
Efavirenz 600 mg QD (Indinavir/ritonavir 800/100 BID)	Indinavir AUC:↓ 25 % Indinavir C_{min} ↓ 50 % (Relative to Indinavir/ritonavir 800/100 BID alone) Ritonavir AUC ↓ 36 % Ritonavir C_{min}:↓ 39 % Efavirenz AUC and C_{min} : ↔	Dose increases of indinavir/ritonavir when given in combination with efavirenz have not been studied.
Anti-Mycobacterial		
Rifabutin	Interaction with indinavir/ritonavir not studied Decreased indinavir concentrations and increased rifabutin concentrations are expected.	No dose recommendations for indinavir/ritonavir with rifabutin could be given, therefore the combination is not recommended. If rifabutin treatment is required, alternative agents for treating HIV infection should be sought.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Rifampicin	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 92 % decrease in indinavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and CRIXIVAN with concomitant low-dose ritonavir is contraindicated (see section 4.3).
Other Anti-infectives		
Atovaquone	Interaction with indinavir/ritonavir not studied Ritonavir induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone.	Careful monitoring of therapeutic and adverse effects is recommended when atovaquone is concomitantly administered with indinavir/ritonavir.
Erythromycin, Itraconazole	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of erythromycin and itraconazole.	Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole are concomitantly administered with indinavir/ritonavir.
Ketoconazole	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of ketoconazole. Co-administration of ritonavir and ketoconazole caused an increased incidence of gastrointestinal and hepatic adverse events.	Careful monitoring of therapeutic and adverse effects is recommended when ketoconazole is concomitantly administered with indinavir/ritonavir. A dose reduction of ketoconazole should be considered when co-administered with indinavir/ritonavir.
ANALGESICS		
Fentanyl	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.	Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with indinavir/ritonavir.
Methadone	Interaction with indinavir/ritonavir not studied There is no significant effect of unboosted indinavir on methadone AUC (see Table 1 above). Decreases in methadone AUC has been observed with other ritonavir-boosted protease inhibitors. Ritonavir may induce glucuronidation of methadone.	Increased methadone dose may be necessary when concomitantly administered with indinavir/ritonavir. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
Morphine	Interaction with indinavir/ritonavir not studied Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir.	Careful monitoring of therapeutic and adverse effects is recommended when morphine is concomitantly administered with indinavir/ritonavir.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTIARRTHYMICS		
Digoxin 0.4 mg SD Ritonavir 200 mg BID	Interaction with indinavir/ritonavir not studied Digoxin AUC: ↑ 22 %	Ritonavir may increase digoxin levels due to modification of P-glycoprotein mediated digoxin efflux. Careful monitoring of digoxin levels is recommended when digoxin is concomitantly administered with indinavir/ritonavir.
ANTICOAGULANT		
Warfarin Ritonavir 400 mg BID	Interaction with indinavir/ritonavir not studied R-warfarin levels may be decreased leading to reduced anticoagulation due to induction of CYP1A2 and CYP2C9 by ritonavir.	Anticoagulation parameters should be monitored when warfarin is coadministered with indinavir/ritonavir.
ANTICONVULSANTS		
Carbamazepine	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of carbamazepine.	Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with indinavir/ritonavir.
Divalproex, lamotrigine, phenytoin	Interaction with indinavir/ritonavir not studied Ritonavir induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants.	Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with indinavir/ritonavir. Phenytoin may decrease serum levels of ritonavir.
ANTIDEPRESSANTS		
Trazodone 50 mg SD Ritonavir 200 mg BID	Interaction with indinavir/ritonavir not studied Trazodone AUC: ↑ 2.4-fold An increase in the incidence in trazodone-related adverse events was noted when coadministered with ritonavir.	The combination of trazodone with indinavir/ritonavir should be used with caution, initiating trazodone at the lowest dose and monitoring for clinical response and tolerability.
ANTIHISTAMINES		
Fexofenadine	Interaction with indinavir/ritonavir not studied Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when coadministered resulting in increased concentrations of fexofenadine.	Careful monitoring of therapeutic and adverse effects is recommended when fexofenadine is concomitantly administered with indinavir/ritonavir.
Loratidine	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of loratidine.	Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with indinavir/ritonavir.
CALCIUM CHANNEL BLOCKERS		
Diltiazem 120 mg QD (Indinavir/ritonavir 800/100 BID)	Diltiazem $AUC_{0\text{-}24hr}$: ↑ 43 % Indinavir/ritonavir AUCs: ↔	Dose modification of calcium channel blockers should be considered when co-administered with indinavir/ritonavir as it may result in an increased response.
Amlodipine 5 mg QD (Indinavir/ritonavir 800/100 BID)	Amlodipine $AUC_{0\text{-}24hr}$: ↑ 80 % Indinavir/ritonavir AUCs: ↔	

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
HMG-CoA REDUCTASE INHIBITORS		Same recommendations as for indinavir without ritonavir boosting (see Table 1).
IMMUNOSUPPRESSIVES		
Cyclosporine A (Indinavir/ritonavir 800/100 BID)	Following initiation of indinavir/ritonavir 800/100 BID or lopinavir/ritonavir 400/100 BID, dose reduction of cyclosporine A to 5-20 % of prior dose was needed to maintain cyclosporine A levels within therapeutic range in one study.	Cyclosporine A dose adjustments should be made according to measured cyclosporine A trough blood levels.
Tacrolimus	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of tacrolimus.	Careful monitoring of therapeutic and adverse effects is recommended when tacrolimus is concomitantly administered with indinavir/ritonavir.
PDE5 INHIBITOR		
Sildenafil, tadalafil	Interaction not studied.	For sildenafil and tadalafil, same recommendations as for indinavir without ritonavir boosting (see Table 1).
Vardenafil	Interaction not studied.	Vardenafil dose should not exceed a maximum of 2.5 mg in a 72-hour period when given with a boosted protease inhibitor.
SEDATIVES/HYPNOTICS		
Buspirone	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of buspirone.	Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with indinavir/ritonavir.
Midazolam (parenteral)	Interaction with indinavir/ritonavir Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally (CYP3A4 inhibition).	CRIXIVAN with ritonavir and oral midazolam should not be coadministered (see section 4.3). Caution should be used with coadministration of CRIXIVAN with ritonavir and parenteral midazolam. If CRIXIVAN with ritonavir is coadministered with parenteral midazolam, it should be done in an intensive care unit with close clinical monitoring in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
STEROIDS		
Dexamethasone	Interaction with indinavir/ritonavir not studied ↑ dexamethasone exposure expected (CYP3A inhibition). ↓ indinavir plasma concentrations may be expected (CYP3A induction).	Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with indinavir/ritonavir.

For information regarding diet or the effect of food on indinavir absorption (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant patients. Indinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Given that 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 (see section 5.2).

Hyperbilirubinaemia, reported predominantly as elevated indirect bilirubin, has occurred in 14 % of patients during treatment with indinavir. Because it is unknown whether indinavir will exacerbate physiologic hyperbilirubinaemia in neonates, careful consideration must be given to the use of indinavir in pregnant women at the time of delivery (see section 4.8).

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.

Breast-feeding
It is recommended that HIV−infected women do 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. Mothers should be instructed to discontinue breast−feeding during treatment.

Fertility
There are no data available regarding potential effects of CRIXIVAN treatment on male or female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

Nephrolithiasis occurred in approximately 10 % of patients treated with the recommended (unboosted) dose of CRIXIVAN in a pooled analysis of controlled clinical trials (see also below table and in section 4.4).

Clinical adverse reactions reported by the investigators as possibly, probably, or definitely related to CRIXIVAN in ≥ 5 % of patients treated with CRIXIVAN monotherapy or in combination with NRTI(s) (n = 309) for 24 weeks are listed below. Many of these adverse reactions were also identified as common pre−existing or frequently occurring medical conditions in this population. These adverse reactions were: nausea (35.3 %), headache (25.2 %), diarrhoea (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 %). With the exception of dry skin, rash, and taste perversion, the incidence of clinical adverse reactions was similar or higher among patients treated with antiretroviral nucleoside analogue controls than among patients treated with CRIXIVAN monotherapy or in combination with NRTI(s). This overall safety profile remained similar for 107 patients treated with CRIXIVAN monotherapy or in combination with NRTI(s) for up to 48 weeks. Adverse reactions, including nephrolithiasis, may lead to treatment interruption.

In controlled clinical trials conducted world–wide, 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 adult 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.

The following adverse reactions have been reported during clinical studies in adults and/or post-marketing use for CRIXIVAN monotherapy and/or CRIXIVAN with combination antiretroviral therapy (CART).

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the available data). Adverse reactions have also been reported during post-marketing experience* as they are derived from spontaneous reports, incidences cannot be determined.

System Organ Class	Frequency	Adverse reactions CRIXIVAN
Blood and lymphatic system disorders	Very common	increases in MCV, decreases in neutrophils
	Not known*	increased spontaneous bleeding in patients with haemophilia, anemia including acute haemolytic anaemia, thrombocytopenia (see section 4.4).
Immune system disorders	Not known*	anaphylactoid reactions
Metabolism and nutrition disorders	Not known*	new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia.
Nervous system disorders	Very common	headache, dizziness
	Common	insomnia, hypoaesthesia; paraesthesia
	Not known*	oral paraesthesia.
Gastrointestinal disorders	Very common	nausea, vomiting, diarrhoea, dyspepsia
	Common	flatulence, dry mouth, acid regurgitation
	Not known*	hepatitis, including reports of hepatic failure, pancreatitis.
Hepato-biliary disorders	Very Common	isolated asymptomatic hyperbilirubinaemia, increased ALT and AST
	Not known*	liver function abnormalities

System Organ Class	Frequency	Adverse reactions CRIXIVAN
Skin and subcutaneous tissue disorders	Very common Common Not known*	rash, dry skin pruritus rash including erythema multiforme and Stevens Johnson syndrome, hypersensitivity vasculitis, alopecia, hyperpigmentation, urticaria; ingrown toenails and/or paronychia.
Musculoskeletal and connective tissue disorders	Common Not known*	myalgia myositis, rhabdomyolysis, increased CPK, osteonecrosis (see section 4.4), periarthritis.
Renal and urinary disorders	Very common Common Not known*	haematuria, proteinuria, crystalluria nephrolithiasis, dysuria nephrolithiasis, in some cases with renal insufficiency or acute renal failure; pyelonephritis, interstitial nephritis, sometimes associated with indinavir crystal deposits. In some patients, resolution of the interstitial nephritis did not occur following discontinuation of indinavir therapy; renal insufficiency, renal failure, leucocyturia (see section 4.4).
General disorders and administration site conditions	Very common	asthenia/fatigue, taste perversion, abdominal pain.

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Description of selected adverse reactions
Nephrolithiasis
Nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), has been reported in approximately 10 % (252/2,577) of patients receiving CRIXIVAN in clinical trials 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).

Hyperbilirubinaemia
Isolated asymptomatic hyperbilirubinaemia (total bilirubin ≥ 2.5 mg/dL, 43 mcmol/L) was reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or

alkaline phosphatase, has occurred in approximately 14 % of patients treated with CRIXIVAN alone or in combination with other antiretroviral agents. Most patients continued treatment with CRIXIVAN without dose reduction and bilirubin values gradually declined toward baseline. Hyperbilirubinaemia occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

Paediatric population
In clinical trials in paediatric patients (≥ 3 years), the adverse reaction profile was similar to that for adult patients except for a higher frequency of nephrolithiasis of 29 % (20/70) in paediatric patients treated with CRIXIVAN. Asymptomatic pyuria of unknown etiology was noted in 10.9 % (6/55) of paediatric patients who received CRIXIVAN. Some of these events were associated with mild elevation of serum creatinine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been reports of human overdose with CRIXIVAN. The most commonly reported symptoms were gastro-intestinal (e.g., nausea, vomiting, diarrhoea) and renal (e.g., nephrolithiasis, flank pain, haematuria).

It is not known whether indinavir is dialyzable by peritoneal or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitor, ATC code JO5AE02

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 (IC_{95}) 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 (NNRTIs). 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 NNRTIs.

Medicinal product resistance
Loss of suppression of viral RNA levels occurred in some patients; however, CD4 cell counts were often sustained above pre–treatment 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 amino acid sites in the protease have been associated with indinavir resistance: L10, K20, L24, M46, I54, L63, I64, A71, V82, I84, and L90. The basis for their contributions to resistance, however, is complex. None of these substitutions was either necessary or sufficient for resistance. For example, no single substitution or pair of substitutions was capable of engendering measurable (≥ four–fold) resistance to indinavir, and the level of resistance was dependent on the ways in which multiple substitutions were combined. In general, however, higher levels of resistance resulted from the co–expression of greater numbers of substitutions at the eleven identified positions. Among patients experiencing viral RNA rebound during indinavir monotherapy at 800 mg q8h, substitutions at only three of these sites were observed in the majority of patients: V82 (to A or F), M46 (to I or L), and L10 (to I or R). Other substitutions were observed less frequently. The observed amino acid substitutions appeared to accumulate sequentially and in no consistent order, probably as a result of ongoing viral replication.

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

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).

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 PIs, 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

Adults

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/mm^3.

In one published study, 20 HIV-infected patients with undetectable plasma viral load (< 200 copies/mL) receiving indinavir 800 mg every 8 hours were switched in an open, cross-over design to indinavir/ritonavir 400/100 mg every 12 hours. Eighteen patients completed the study to week 48. Viral load remained < 200 copies/mL for 48 weeks in all patients.

Another published study evaluated the efficacy and safety of indinavir/ritonavir 400/100 mg every 12 hours in 40 antiretroviral-naïve patients. Thirty subjects completed 48 weeks of treatment. At week 4, the indinavir Cmin was 500 ng/mL with substantial trough variability (range 5 to 8,100 ng/mL). By intent to treat analysis 65 % of patients had HIV RNA < 400 copies/mL and 50 % had viral load < 50 copies/mL; by on-treatment analysis 96 % of patients had HIV RNA < 400 copies/mL and 74 % had viral load < 50 copies/mL.

Eighty antiretroviral naïve patients were entered into a third published study. In this open label non-randomized single arm study, patients were treated with stavudine and lamivudine plus indinavir/ritonavir 400/100 mg every 12 hours. Sixty-two patients completed the study to week 96. In the intent to treat and on treatment analyses the proportion of patients with HIV RNA of < 50 copies/mL was 68.8 % and 88.7 %, respectively, at week 96.

Indinavir alone or in combination with nucleoside analogues (zidovudine/stavudine and lamivudine) has been shown to delay clinical progression rate compared with nucleoside analogues and to provide a sustained effect on viral load and CD4 count.

In zidovudine experienced patients, indinavir, zidovudine and lamivudine in combination compared with lamivudine added to zidovudine reduced the probability of AIDS defining illness or death (ADID) at 48 weeks from 13 % to 7 %. Similarly, in antiretroviral naive patients, indinavir with and without zidovudine compared with zidovudine alone reduced the probability of ADID at 48 weeks from 15 % with zidovudine alone to approximately 6 % with indinavir alone or in combination with zidovudine.

Effects on viral load were consistently more pronounced in patients treated with indinavir in combination with nucleoside analogues, but the proportion of patients with serum viral RNA below the limit of quantification (500 copies/mL) varied between studies, at week 24 from 40 % to more than 80 %. This proportion tends to remain stable over prolonged periods of follow–up. Similarly, effects on CD4 cell count tend to be more pronounced in patients treated with indinavir in combination with nucleoside analogues compared with indinavir alone. Within studies, this effect is sustained also after prolonged periods of follow–up.

Paediatric population

Two clinical trials in 41 paediatric patients (4 to 15 years of age) were designed to characterise the safety, antiretroviral activity, and pharmacokinetics of indinavir in combination with stavudine and lamivudine. In one study, at week 24, the proportion of patients with plasma viral RNA below 400 copies/mL was 60 %; the mean increase in CD4 cell counts was 242 cells/mm^3; and the mean increase in percent CD4 cell counts was 4.2 %. At week 60, the proportion of patients with plasma viral RNA below 400 copies/mL was 59 %. In another study, at week 16, the proportion of patients with plasma viral RNA below 400 copies/mL was 59 %; the mean increase in CD4 cell counts was 73 cells/mm^3; and the mean increase in percent CD4 cell counts was 1.2 %. At week 24, the proportion of patients with plasma viral RNA below 400 copies/mL was 60 %.

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 1,000–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. The bioavailability of a single 800–mg dose of indinavir was approximately 65 % (90 % CI, 58 – 72 %).

Data from a steady state study in healthy volunteers indicate that there is a diurnal variation in the pharmacokinetics of indinavir. Following a dose regimen of 800 mg every 8 hours, measured peak plasma concentrations (C_{max}) after morning, afternoon and evening doses were 15,550 nM, 8,720 nM and 8,880 nM, respectively. Corresponding plasma concentrations at 8 hours post dose were 220 nM, 210 nM and 370 nM, respectively. The relevance of these findings for ritonavir boosted indinavir is unknown. At steady state following a dose regimen of 800 mg every 8 hours, HIV–seropositive adult patients in one study achieved geometric means of: $AUC_{0\text{-}8h}$ of 27,813 nM*h (90 % confidence interval = 22,185, 34,869), peak plasma concentrations 11,144 nM (90 % confidence interval = 9,192, 13,512) and plasma concentrations at 8 hours post dose 211 nM (90 % confidence interval = 163, 274).

Food effect
At steady state following a dose regimen of 800 mg/100 mg of indinavir/ritonavir every 12 hours with a low-fat meal, healthy volunteers in one study achieved geometric means: AUC_{0-12h} 116,067 nM*h (90 % confidence interval = 101,680, 132,490), peak plasma concentrations 19,001 nM (90 % confidence interval = 17,538, 20,588), and plasma concentrations at 12 hours post dose 2,274 nM (90 % confidence interval = 1,701, 3,042). No significant difference in exposure was seen when the regimen was given with a high-fat meal.

Indinavir boosted regimen. Limited data are available on the pharmacokinetics of indinavir in association with low dose ritonavir. The pharmacokinetics of indinavir (400 mg) with ritonavir (100 mg) dosed twice daily was examined in two studies. Pharmacokinetic analysis in one study was performed on nineteen of the patients, with a median (range) indinavir AUC 0-12hr, Cmax, and Cmin of 25,421 nM*h (21,489 – 36,236 nM*h), 5,758 nM (5,056 – 6,742 nM) and 239 (169 – 421 nM), respectively. The pharmacokinetic parameters in the second study were comparable.

In HIV–infected paediatric patients, a dose regimen of indinavir hard capsules, 500 mg/m^2 every 8 hours, produced $AUC_{0–8hr}$ values of 27,412 nM*h, peak plasma concentrations of 12,182 nM, and plasma concentrations at 8 hours post dose of 122 nM. The AUC and peak plasma concentrations were generally similar to those previously observed in HIV–infected adults receiving the recommended dose of 800 mg every 8 hours; it should be observed that the plasma concentrations 8 hours post dose were lower.

During pregnancy, it has been demonstrated that the systemic exposure of indinavir is relevantly decreased (PACTG 358. Crixivan, 800 mg every 8 hours + zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day). The mean indinavir plasma AUC_{0-8hr} at week 30-32 of gestation (n = 11) was 9,231 nM∗hr, which is 74 % (95 % CI: 50 %, 86 %) lower than that observed 6 weeks postpartum. Six of these 11 (55 %) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in non-pregnant patients in another study (see section 4.6).

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.

The pharmacokinetics of indinavir taken as indinavir sulphate salt (from opened hard capsules) mixed in apple sauce were generally comparable to the pharmacokinetics of indinavir taken as hard capsules, under fasting conditions. In HIV–infected paediatric patients, the pharmacokinetic parameters of indinavir in apple sauce were: $AUC_{0–8hr}$ of 26,980 nM*h; peak plasma concentration of 13,711 nM; and plasma concentration at 8 hours post dose of 146 nM.

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 proteinase inhibitory activity.

Elimination
Over the 200–1,000–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 medicinal product following single dose administration in the fasted state was 10.4 % following a 700–mg dose, and 12.0 % following a 1,000–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 race.

There are no clinically significant differences in the pharmacokinetics of indinavir in HIV seropositive women compared to HIV seropositive men.

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.

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 medicinal product –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 5,000 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
No carcinogenicity was noted in mice at the maximum tolerated dose, which corresponded to a systemic exposure approximately 2 to 3 times higher than the clinical exposure. In rats, at similar exposure levels, an increased incidence of thyroid adenomas was seen, probably related to an increase in release of thyroid stimulating hormone secondary to an increase in thyroxine clearance. The relevance of the findings to humans is likely limited.

Developmental Toxicity
Developmental toxicity studies were performed in rats, rabbits and dogs (at doses which produced systemic exposures comparable to or slightly greater than human exposure) and revealed no evidence of teratogenicity. No external or visceral changes were observed in rats, however, increases in the incidence of supernumerary ribs and of cervical ribs were seen. No external, visceral, or skeletal changes were observed in rabbits or dogs. In rats and rabbits, no effects on embryonic/foetal survival or foetal weights were observed. In dogs, a slight increase in resorptions was seen; however, all

foetuses in medication–treated animals were viable, and the incidence of live foetuses in medication–treated animals was comparable to that in controls.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
anhydrous lactose
magnesium stearate

Capsule shell:
gelatin
titanium dioxide (E 171)
printing ink: indigo carmine (E 132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle with a polypropylene cap and a foil induction cap containing 180, 270 or 360 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The bottles contain desiccant canisters that should remain in the container.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/001
EU/1/96/024/002
EU/1/96/024/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 October 1996
Date of latest renewal: 18 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 400 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.

Excipient with known effect
Each 400 mg capsule contains 149.6 mg of lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule.

The capsules are semi–translucent white and coded 'CRIXIVAN 400 mg' in green.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRIXIVAN is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV–1 infected adults.

4.2 Posology and method of administration

CRIXIVAN should be administered by physicians who are experienced in the treatment of HIV infection. On the basis of current pharmacodynamic data, indinavir must be used in combination with other antiretroviral agents. When indinavir is administered as monotherapy resistant viruses rapidly emerge (see section 5.1).

Posology
The recommended dose of indinavir is 800 mg orally every 8 hours.

Data from published studies suggest that CRIXIVAN 400 mg in combination with ritonavir 100 mg, both administered orally twice daily, may be an alternative dosing regimen. The suggestion is based on limited published data (see section 5.2).

A dose reduction of indinavir to 600 mg every 8 hours should be considered when administering itraconazole or ketoconazole concurrently (see section 4.5).

Special populations
Hepatic impairment
In patients with mild–to–moderate hepatic impairment due to cirrhosis, the dose of indinavir should be reduced to 600 mg every 8 hours. The recommendation is based on limited pharmacokinetic data (see section 5.2). Patients with severe hepatic impairment have not been studied; therefore, no dosing recommendations can be made (see section 4.4).

Renal impairment
Safety in patients with impaired renal function has not been studied; however, less than 20 % of indinavir is excreted in the urine as unchanged medicinal product or metabolites (see section 4.4).

Paediatric population
The safety and efficacy of CRIXIVAN in children under the age of 4 years have not been established (see sections 5.1 and 5.2). Currently available data in children above the age of 4 years are described in sections 4.8, 5.1, and 5.2.

Method of administration
The hard 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.

If co-administered with ritonavir, CRIXIVAN may be administered with or without food.

To ensure adequate hydration, it is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Indinavir with or without ritonavir should not be administered concurrently with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4. Inhibition of CYP3A4 by both CRIXIVAN and ritonavir could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see section 4.5).

CRIXIVAN with or without ritonavir should not be administered concurrently with amiodarone, terfenadine, cisapride, astemizole, quetiapine, alprazolam, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), pimozide, ergot derivatives, simvastatin or lovastatin (see section 4.4).

Combination of rifampicin with CRIXIVAN with or without concomitant low-dose ritonavir is contraindicated (see section 4.5). Concurrent use of indinavir with herbal preparations containing St John's wort (Hypericum perforatum) is contraindicated (see section 4.5).

In addition, indinavir with ritonavir must not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Indinavir must not be given with ritonavir to patients with decompensated liver disease as ritonavir is principally metabolized and eliminated by the liver (see section 4.4).

When CRIXIVAN is used with ritonavir, consult the Summary of Product Characteristics of ritonavir for additional contraindications.

4.4 Special warnings and precautions for use

Nephrolithiasis and tubulointerstitial nephritis
Nephrolithiasis has occurred with indinavir therapy in adult patients with a cumulative frequency of 12.4 % (range across individual trials: 4.7 % to 34.4 %). The cumulative frequency of nephrolithiasis events increases with increasing exposure to CRIXIVAN; however, the risk over time remains relatively constant. In some cases, nephrolithiasis 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. for 1–3 days) during the acute episode of nephrolithiasis or discontinuation of therapy may be considered. Evaluation may consist of urinalysis, serum BUN and creatinine, and ultrasound of the bladder and kidneys. Adequate hydration is recommended in all patients on indinavir (see sections 4.2 and 4.8).

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

Cases of interstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leucocyturia (> 100 cells/high power field). In patients at increased risk, urinary screening should be considered. If persistent severe leucocyturia is found, further investigation might be warranted.

Medicinal product interactions
Indinavir should be used cautiously with other medicinal products that are potent inducers of CYP3A4. Co–administration may result in decreased plasma concentrations of indinavir and as a consequence an increased risk for suboptimal treatment and facilitation of development of resistance (see section 4.5).

If indinavir is given with ritonavir, the potential interaction may be increased. The Interactions section of the SPC for ritonavir should also be consulted for information about potential interactions.

Atazanavir as well as indinavir are associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UDP-glucuronosyltransferase (UGT). Combinations of atazanavir with or without ritonavir and Crixivan have not been studied and co-administration of these medicinal products is not recommended due to risk of worsening of these adverse reactions.

Concomitant use of indinavir with lovastatin or simvastatin is not recommended 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 must also be exercised if indinavir is used concurrently with atorvastatin. The interaction of indinavir or indinavir/ritonavir with pravastatin or fluvastatin is not known (see section 4.5).

Co–administration of CRIXIVAN with sildenafil, tadalafil and vardenafil (PDE5 inhibitors) are 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 section 4.5).

HIV Transmission
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 indinavir.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease
The safety and efficacy of indinavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

An increased incidence of nephrolithiasis has been observed in patients with underlying liver disorders when treated with indinavir.

Immune Reactivation Syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Patients with coexisting conditions
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with PIs. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with PIs was continued or re-introduced 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.

Patients with mild–to–moderate hepatic insufficiency due to cirrhosis will require a dose reduction of indinavir due to decreased metabolism of indinavir (see section 4.2). 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 medicinal product or metabolites (see section 4.2).

Osteonecrosis:
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lactose
This medicinal product contains 299.2 mg of lactose in each 800 mg dose (maximum single dose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of indinavir is mediated by the cytochrome P450 enzyme CYP3A4. Therefore, other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of indinavir. Similarly, indinavir might also modify the pharmacokinetics of other substances that share this metabolic pathway. Boosted indinavir (indinavir with ritonavir) may have additive pharmacokinetic effects on substances that share the CYP3A4 pathway as both ritonavir and indinavir inhibit the cytochrome P450 enzyme CYP3A4.

Indinavir with or without ritonavir should not be administered concurrently with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4. Inhibition of CYP3A4 by both CRIXIVAN and ritonavir could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions. CRIXIVAN with or without ritonavir should not be administered concurrently with amiodarone, terfenadine, cisapride, astemizole, quetiapine, alprazolam, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see Table 1 and 2 below), pimozide, ergot derivatives, simvastatin or lovastatin. In addition, indinavir with ritonavir should not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Concurrent use of indinavir with rifampicin or herbal preparations containing St John's wort (Hypericum perforatum) is contraindicated.

Medicinal products listed above are not repeated in Table 1 and 2 unless specific interaction data is available.

Refer also to sections 4.2 and 4.3.

Table 1. Interactions and dose recommendations with other medical products – <u>UNBOOSTED INDINAVIR</u>

Interactions between indinavir and other medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change (≤ +/- 20 %) as "↔", single dose as "SD", once daily as "QD", twice daily as "BID", three times daily as "TID", and four times daily as "QID").

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Didanosine Formulation with buffer	No formal interaction study has been performed. 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. Antiretroviral activity was unaltered when didanosine was administered 3 hours after treatment with indinavir.	Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach.
Didanosine enteric-coated 400 mg SD (Indinavir 800 mg SD)	Indinavir: ↔ (Relative to Indinavir 800 mg SD alone) Didanosine: ↔	Can be administered without any restrictions with respect to time of administration or food.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Stavudine 40 mg BID (Indinavir 800 mg TID)	Indinavir AUC: ↔ Indinavir C_{min} :↔ (Relative to Indinavir 800 mg TID alone) Stavudine AUC: ↑ 21 % Stavudine C_{min}: not evaluated	Indinavir and NRTIs can be co-administered without dose adjustment.
Zidovudine 200 mg TID (Indinavir 1,000 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↔ (Relative to Indinavir 1,000 mg TID alone) Zidovudine AUC: ↔ Zidovudine C_{min}: ↑ 51 %	
Zidovudine/Lamivudine 200/150 mg TID (Indinavir 800 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↔ (Relative to Indinavir 800 mg TID alone) Zidovudine AUC: ↑ 39 % Zidovudine C_{min}: ↔ Lamivudine AUC: ↔ Lamivudine C_{min}: ↔	
NNRTIs		
Delavirdine 400 mg TID (Indinavir 600 mg TID) Delavirdine 400 mg TID Indinavir 400 mg TID	Indinavir AUC: ↑ 53 % Indinavir C_{min} ↑ 298 % (Relative to Indinavir 800 mg TID alone) Indinavir AUC: ↔ Indinavir C_{min}: ↑ 118 % (Relative to Indinavir 800 mg TID alone) Delavirdine: ↔	Dose reduction of CRIXIVAN to 400-600 mg every 8 hours should be considered.
Efavirenz 600 mg QD (Indinavir 1,000 mg TID) Efavirenz 200 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↓ 46 % Indinavir C_{min}: ↓ 57 % (Relative to Indinavir 800 mg TID alone) An increased dose (1,000 mg TID) of indinavir does not compensate for the inducing effect of efavirenz. Indinavir AUC: ↓ 31 % Indinavir C_{min}: ↓ 40 % Efavirenz AUC: ↔	No specific dose recommendation can be given.
Nevirapine 200 mg BID (Indinavir 800 mg TID)	Indinavir AUC: ↓ 28 % Nevirapine: ↔ (CYP3A induction)	A dose increase of indinavir to 1,000 mg every 8 hours should be considered if given with nevirapine.
PIs		
Amprenavir 1,200 mg BID (Indinavir 1,200 mg BID)	Amprenavir AUC: ↑ 90 % Indinavir: ↔	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Atazanavir	Interaction not studied	Combination of atazanavir with or without ritonavir and Crixivan are not recommended due to increased risk of hyperbilirubinemia (see section 4.4).
Ritonavir 100 mg BID (Indinavir 800 mg BID) Ritonavir 200 mg BID (Indinavir 800 mg BID) Ritonavir 400 mg BID (Indinavir 800 mg BID) Ritonavir 400 mg BID (Indinavir 400 mg BID) Ritonavir 100 mg BID (Indinavir 400 mg BID)	Indinavir AUC_{24hr}:↑ 178 *%* Indinavir C_{min}:↑11-fold; (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC: ↑ 72 % Ritonavir C_{min}: ↑ 62 % Indinavir AUC_{24hr}:↑266 % Indinavir C_{min}:↑24-fold; (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC: ↑ 96 % Ritonavir C_{min}: ↑ 371 % Indinavir AUC_{24hr}:↑220 % Indinavir C_{min}:↑ 24-fold (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC_{24hr}: ↔ Indinavir AUC_{24hr}:↑68 % Indinavir C_{min}: ↑ 10-fold (Relative to Indinavir 800 mg TID alone*) Ritonavir AUC_{24hr}: ↔ Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 800 mg TID alone*) (*historical controls	The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Preliminary clinical data suggest that CRIXIVAN 400 mg in combination with ritonavir 100 mg, both administered orally twice daily, may be an alternative dosing regimen (see section 5.2). A boosted dose of 800 mg indinavir/100 mg ritonavir twice daily results in increased risk of adverse events.
Saquinavir 600 mg SD (hard gel capsule formulation) (Indinavir 800 mg TID) Saquinavir 800 mg SD (soft gel capsule formulation) (Indinavir 800 mg TID) Saquinavir 1,200 mg SD (soft gel capsule formulation) (Indinavir 800 mg TID)	Saquinavir AUC: ↑ 500 % Saquinavir C_{min}: ↑ 190 % (Relative to saquinavir 600 mg SD (hard gel formulation) alone) Saquinavir AUC: ↑ 620 % Saquinavir C_{min}: ↑ 450 % (Relative to saquinavir 800 mg SD (soft gel formulation) alone) Saquinavir AUC: ↑ 360 % Saquinavir C_{min}: ↑ 450 % (Relative to saquinavir 1,200 mg (soft gel formulation) alone) The design of the study does not allow for definitive evaluation of the effect of saquinavir on indinavir, but suggests there is less than a two–fold increase in indinavir AUC_{8h} during co–administration with saquinavir	The appropriate doses for this combination, with respect to efficacy and safety, have not been established.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Antibiotics		
Sulphamethoxazole/ Trimethoprim 800 mg/160 mg BID (Indinavir 400 mg QID)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg QID alone) Sulphamethoxazole AUC and C_{min}: ↔	Indinavir and sulphamethoxazole/ trimethoprim can be co-administered without dose adjustment.
Antifungals		
Fluconazole 400 mg QD (Indinavir 1,000 mg TID)	Indinavir AUC: ↓ 24 % Indinavir C_{min}: ↔ (Relative to Indinavir 1,000 mg TID alone)	Indinavir and fluconazole can be co-administered without dose adjustment.
Itraconazole 200 mg BID (Indinavir 600 mg TID)	Indinavir AUC: ↔ Indinavir C_{min}: ↑ 49 % (Relative to Indinavir 800 mg TID alone)	Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended with administering itraconazole concurrently.
Ketoconazole 400 mg QD (Indinavir 600 mg TID) Ketoconazole 400 mg QD (Indinavir 400 mg TID)	Indinavir AUC: ↓ 20 % Indinavir C_{min}: ↑ 29 % (Relative to Indinavir 800 mg TID alone) Indinavir AUC ↓ 56 % Indinavir C_{min} ↓ 27 % (Relative to Indinavir 800 mg TID alone)	Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.
Anti-Mycobacterial		
Isoniazid 300 mg QD (Indinavir 800 mg TID)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 800 mg TID alone) Isoniazid AUC and C_{min}: ↔	Indinavir and isoniazid can be co-administered without dose adjustment.
Rifabutin 300 mg QD (Indinavir 800 mg TID) Rifabutin 150 mg QD (Indinavir 800 mg TID)	Indinavir AUC ↓ 34 % Indinavir C_{min} : ↓ 39 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC: ↑ 173 % Rifabutin C_{min}: ↑ 244 % (Relative to rifabutin 300 mg QD alone) Indinavir AUC: ↓ 32 % Indinavir C_{min}: ↓ 40 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC*: ↑ 54 % Rifabutin C_{min*}: ↑ 99 % (*Relative to rifabutin 300 mg QD alone. No data has been obtained comparing rifabutin 150 mg QD in combination with indinavir 800 mg TID with a reference dose of 150 mg rifabutin alone)	Dose reduction of rifabutin and dose increase of Crixivan has not been confirmed in clinical studies. Therefore co-administration is not recommended. If rifabutin treatment is required, alternative agents for treating HIV infection should be sought.
Rifampicin 600 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↓ 92 % (Relative to Indinavir 800 mg TID alone) This effect is due to an induction of CYP3A4 by rifampicin.	The use of rifampicin with indinavir is contraindicated.
ANALGESICS		
Methadone 20-60 mg QD (Indinavir 800 mg TID)	Indinavir AUC: ↔ (Relative to Indinavir 800 mg TID historical controls) Methadone AUC and C_{min}: ↔	Indinavir and methadone can be co-administered without dose adjustment.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTIARRHYTHMICS		
Quinidine 200 mg SD (Indinavir 400 mg SD)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg SD) ↑ Quinidine concentration expected (CYP3A4 inhibition by indinavir)	Caution is warranted and therapeutic concentration monitoring is recommended for quinidine when coadministered with CRIXIVAN. The use of indinavir/ritonavir with quinidine is contraindicated.
ANTIASTHMATIC		
Theophylline 250 mg SD (Indinavir 800 mg TID)	Theophylline AUC and C_{min}: ↔	Indinavir and theophylline can be co-administered without dose adjustment.
ANTICOAGULANT		
Warfarin	Not studied, combined administration may result in increased warfarin levels.	Dose adjustment of warfarin may be required.
ANTICONVULSANTS		
Carbamazepine, phenobarbital phenytoin	Indinavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of these anticonvulsants. Concomitant use of medicinal products that are inducers of CYP3A4, such as carbamazepine, phenobarbital and phenytoin may reduce indinavir plasma concentrations.	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with indinavir.
ANTIDEPRESSANTS		
Venlafaxine 50 mg TID (Indinavir 800 mg SD)	Indinavir AUC: ↓ 28 % (Relative to Indinavir 800 mg SD alone) Venlafaxine and active metabolite O-desmethyl-venlafaxine: ↔	The clinical significance of this finding is unknown.
ANTIPSYCHOTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by indinavir, concentrations of quetiapine are expected to increase.	Concomitant administration of indinavir and quetiapine may increase plasma concentrations of quetiapine leading to quetiapine-related toxicity, including coma. Co-administration of quetiapine with indinavir is contraindicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS		
Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blocker concentration Calcium channel blockers are metabolized by CYP3A4 which is inhibited by indinavir.	Caution is warranted and clinical monitoring of patients is recommended.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
HERBAL MEDICATIONS		
St. John's wort (Hypericum perforatum) 300 mg TID (Indinavir 800 mg TID)	Indinavir AUC: ↓ 54 % Indinavir C_{min}: ↓ 81 % (Relative to Indinavir 800 mg TID alone) Reduction in indinavir concentrations due to induction of medicinal product metabolising and/or transport proteins by St. John's wort.	Herbal preparations containing St. John's wort are contraindicated with Crixivan. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible indinavir levels. Indinavir levels may increase on stopping St. John's wort, and the dose of CRIXIVAN may need adjusting. The inducing effect may persist up to 2 weeks after cessation of treatment with St. John's wort.
HISTAMINE H_2 ANTAGONIST		
Cimetidine 600 mg BID (Indinavir 400 mg SD)	Indinavir AUC and C_{min}: ↔ (Relative to Indinavir 400 mg SD alone)	Indinavir and cimetidine can be co-administered without dose adjustment.
HMG-CoA REDUCTASE INHIBITORS		
Lovastatin, simvastatin	Indinavir inhibits CYP3A4 and as a result is expected to markedly increase the plasma concentrations of these HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism.	Combination contraindicated due to an increased risk of myopathy including rhabdomyolysis.
Rosuvastatin	Interaction not studied. Interaction study with Lopinavir/ritonavir + rosuvastatin: Rosuvastatin AUC ↑ 2.08-fold Rosuvastatin Cmax ↑ 4.66-fold (Mechanism unknown)	Combination not recommended
Atorvastatin	↑ atorvastatin concentration Atorvastatin is less dependent on CYP3A4 for metabolism than lovastatin or simvastatin	Use the lowest possible dose of atorvastatin with careful monitoring. Caution is advised.
Pravastatin, fluvastatin	Interaction not studied Metabolism of pravastatin and fluvastatin is not dependent on CYP3A4. Interaction via effects on transport proteins cannot be excluded.	Interaction unknown. If no alternative treatment is available, use with careful monitoring.
IMMUNOSUPPRESSIVES		
Cyclosporine A	Cyclosporine A (CsA) levels markedly increase in patients on PIs, including indinavir.	CsA levels require progressive dose adjustment using therapeutic medicinal product monitoring.
ORAL CONTRACEPTIVES		
Norethindrone/ethinyl estradiol 1/35 1 mcg QD (Indinavir 800 mg TID)	Norethindrone AUC: ↑ 26 % Norethindrone C_{min}: ↑ 44 %	Indinavir and norethindrone/ethinyl estradiol 1/35 can be co-administered without dose adjustment.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
PDE5 INHIBITOR		
Sildenafil 25 mg SD (Indinavir 800 mg TID)	Indinavir AUC: ↑ 11 % Sildenafil AUC ↑ 340 % Coadministration of CRIXIVAN with sildenafil is likely to result in an increase of sildenafil by competitive inhibition of metabolism.	Sildenafil dose should not exceed a maximum of 25 mg in a 48-hour period in patients receiving concomitant indinavir therapy.
Vardenafil 10 mg SD (Indinavir 800 mg TID)	Vardenafil AUC: ↑ 16-fold Coadministration of CRIXIVAN with vardenafil is likely to result in an increase of vardenafil by competitive inhibition of metabolism.	Vardenafil dose should not exceed a maximum of 2.5 mg in a 24-hour period in patients receiving concomitant indinavir therapy.
Tadalafil	Interaction not studied Coadministration of CRIXIVAN with tadalafil is likely to result in an increase of tadalafil by competitive inhibition of metabolism.	Tadalafil dose should not exceed a maximum of 10 mg in a 72 hour period in patients receiving concomitant indinavir therapy.
SEDATIVES/HYPNOTICS		
Midazolam (parenteral)	Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally. Midazolam is extensively metabolized by CYP3A4.	CRIXIVAN and oral midazolam should not be coadministered (see section 4.3). Caution should be used with coadministration of CRIXIVAN and parenteral midazolam. If CRIXIVAN is coadministered with parenteral midazolam, it should be done in an intensive care unit with close clinical monitoring in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
STEROIDS		
Dexamethasone	Interaction not studied ↑ dexamethasone exposure expected (CYP3A inhibition). ↓ indinavir plasma concentrations may be expected (CYP3A induction).	Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with indinavir.

Table 2. Interactions and dose recommendations with other medical products – <u>INDINAVIR BOOSTED WITH RITONAVIR.</u> *No specific interaction studies have been performed with the boosted dose 400 mg indinavir with 100 mg ritonavir.*

Interactions between indinavir/ritonavir and other medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change (≤ +/- 20 %) as "↔", single dose as "SD", once daily as "QD", twice daily as "BID", three times daily as "TID", and four times daily as "QID").

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
Amprenavir	Amprenavir 1,200 mg BID AUC ↑90 % with 800 mg TID indinavir alone (see Table 1). Amprenavir 600 mg BID AUC ↑ 64 % with 100 mg BID ritonavir alone (relative to amprenavir 1,200 mg BID alone). Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. There are no interaction data available on the coadministration of indinavir/ritonavir and amprenavir.	The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Ritonavir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations.
Efavirenz 600 mg QD (Indinavir/ritonavir 800/100 BID)	Indinavir AUC:↓ 25 % Indinavir C_{min} ↓ 50 % (Relative to Indinavir/ritonavir 800/100 BID alone) Ritonavir AUC ↓ 36 % Ritonavir C_{min}:↓ 39 % Efavirenz AUC and C_{min} ↔	Dose increases of indinavir/ritonavir when given in combination with efavirenz have not been studied.
Anti-Mycobacterial		
Rifabutin	Interaction with indinavir/ritonavir not studied Decreased indinavir concentrations and increased rifabutin concentrations are expected.	No dose recommendations for indinavir/ritonavir with rifabutin could be given, therefore the combination is not recommended. If rifabutin treatment is required, alternative agents for treating HIV infection should be sought.
Rifampicin	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 92 % decrease in indinavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and CRIXIVAN with concomitant low-dose ritonavir is contraindicated (see section 4.3).
Other Anti-infectives		
Atovaquone	Interaction with indinavir/ritonavir not studied Ritonavir induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone.	Careful monitoring of therapeutic and adverse effects is recommended when atovaquone is concomitantly administered with indinavir/ritonavir.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Erythromycin, Itraconazole	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of erythromycin and itraconazole.	Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole are concomitantly administered with indinavir/ritonavir.
Ketoconazole	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of ketoconazole. Co-administration of ritonavir and ketoconazole caused an increased incidence of gastrointestinal and hepatic adverse events.	Careful monitoring of therapeutic and adverse effects is recommended when ketoconazole is concomitantly administered with indinavir/ritonavir. A dose reduction of ketoconazole should be considered when co-administered with indinavir/ritonavir.
ANALGESICS		
Fentanyl	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.	Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with indinavir/ritonavir.
Methadone	Interaction with indinavir/ritonavir not studied There is no significant effect of unboosted indinavir on methadone AUC (see Table 1 above). Decreases in methadone AUC has been observed with other ritonavir-boosted protease inhibitors. Ritonavir may induce glucuronidation of methadone.	Increased methadone dose may be necessary when concomitantly administered with indinavir/ritonavir. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
Morphine	Interaction with indinavir/ritonavir not studied Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir.	Careful monitoring of therapeutic and adverse effects is recommended when morphine is concomitantly administered with indinavir/ritonavir.
ANTIARRTHYMICS		
Digoxin 0.4 mg SD Ritonavir 200 mg BID	Interaction with indinavir/ritonavir not studied Digoxin AUC: ↑ 22 %	Ritonavir may increase digoxin levels due to modification of P-glycoprotein mediated digoxin efflux. Careful monitoring of digoxin levels is recommended when digoxin is concomitantly administered with indinavir/ritonavir.
ANTICOAGULANT		
Warfarin Ritonavir 400 mg BID	Interaction with indinavir/ritonavir not studied R-warfarin levels may be decreased leading to reduced anticoagulation due to induction of CYP1A2 and CYP2C9 by ritonavir.	Anticoagulation parameters should be monitored when warfarin is coadministered with indinavir/ritonavir.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTICONVULSANTS		
Carbamazepine	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of carbamazepine.	Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with indinavir/ritonavir.
Divalproex, lamotrigine, phenytoin	Interaction with indinavir/ritonavir not studied Ritonavir induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants.	Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with indinavir/ritonavir. Phenytoin may decrease serum levels of ritonavir.
ANTIDEPRESSANTS		
Trazodone 50 mg SD Ritonavir 200 mg BID	Interaction with indinavir/ritonavir not studied Trazodone AUC: ↑ 2.4-fold An increase in the incidence in trazodone-related adverse events was noted when coadministered with ritonavir.	The combination of trazodone with indinavir/ritonavir should be used with caution, initiating trazodone at the lowest dose and monitoring for clinical response and tolerability.
ANTIHISTAMINES		
Fexofenadine	Interaction with indinavir/ritonavir not studied Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when coadministered resulting in increased concentrations of fexofenadine.	Careful monitoring of therapeutic and adverse effects is recommended when fexofenadine is concomitantly administered with indinavir/ritonavir.
Loratidine	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of loratidine.	Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with indinavir/ritonavir.
CALCIUM CHANNEL BLOCKERS		
Diltiazem 120 mg QD (Indinavir/ritonavir 800/100 BID)	Diltiazem $AUC_{0\text{-}24hr}$: ↑ 43 % Indinavir/ritonavir AUCs: ↔	Dose modification of calcium channel blockers should be considered when co-administered with indinavir/ritonavir as it may result in an increased response.
Amlodipine 5 mg QD (Indinavir/ritonavir 800/100 BID)	Amlodipine $AUC_{0\text{-}24hr}$: ↑ 80 % Indinavir/ritonavir AUCs: ↔	
HMG-CoA REDUCTASE INHIBITORS		Same recommendations as for indinavir without ritonavir boosting (see Table 1).
IMMUNOSUPPRESSIVES		
Cyclosporine A (Indinavir/ritonavir 800/100 BID)	Following initiation of indinavir/ritonavir 800/100 BID or lopinavir/ritonavir 400/100 BID, dose reduction of cyclosporine A to 5-20 % of prior dose was needed to maintain cyclosporine A levels within therapeutic range in one study.	Cyclosporine A dose adjustments should be made according to measured cyclosporine A trough blood levels.
Tacrolimus	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of tacrolimus.	Careful monitoring of therapeutic and adverse effects is recommended when tacrolimus is concomitantly administered with indinavir/ritonavir.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
PDE5 INHIBITOR		
Sildenafil, tadalafil	Interaction not studied.	For sildenafil and tadalafil, same recommendations as for indinavir without ritonavir boosting (see Table 1).
Vardenafil	Interaction not studied.	Vardenafil dose should not exceed a maximum of 2.5 mg in a 72-hour period when given with a boosted protease inhibitor.
SEDATIVES/HYPNOTICS		
Buspirone	Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of buspirone.	Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with indinavir/ritonavir.
Midazolam (parenteral)	Interaction with indinavir/ritonavir Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally (CYP3A4 inhibition).	CRIXIVAN with ritonavir and oral midazolam should not be coadministered (see section 4.3). Caution should be used with coadministration of CRIXIVAN with ritonavir and parenteral midazolam. If CRIXIVAN with ritonavir is coadministered with parenteral midazolam, it should be done in an intensive care unit with close clinical monitoring in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
STEROIDS		
Dexamethasone	Interaction with indinavir/ritonavir not studied ↑ dexamethasone exposure expected (CYP3A inhibition). ↓ indinavir plasma concentrations may be expected (CYP3A induction).	Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with indinavir/ritonavir.

For information regarding diet or the effect of food on indinavir absorption (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant patients. Indinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Given that 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 (see section 5.2).

Hyperbilirubinaemia, reported predominantly as elevated indirect bilirubin, has occurred in 14 % of patients during treatment with indinavir. Because it is unknown whether indinavir will exacerbate

physiologic hyperbilirubinaemia in neonates, careful consideration must be given to the use of indinavir in pregnant women at the time of delivery (see section 4.8).

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.

Breast-feeding
It is recommended that HIV–infected women do 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. Mothers should be instructed to discontinue breast–feeding during treatment.

Fertility
There are no data available regarding potential effects of CRIXIVAN treatment on male or female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

Nephrolithiasis occurred in approximately 10 % of patients treated with the recommended (unboosted) dose of CRIXIVAN in a pooled analysis of controlled clinical trials (see also below table and in section 4.4).

Clinical adverse reactions reported by the investigators as possibly, probably, or definitely related to CRIXIVAN in ≥ 5 % of patients treated with CRIXIVAN monotherapy or in combination with NRTI(s) (n = 309) for 24 weeks are listed below. Many of these adverse reactions were also identified as common pre–existing or frequently occurring medical conditions in this population. These adverse reactions were: nausea (35.3 %), headache (25.2 %), diarrhoea (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 %). With the exception of dry skin, rash, and taste perversion, the incidence of clinical adverse reactions was similar or higher among patients treated with antiretroviral nucleoside analogue controls than among patients treated with CRIXIVAN monotherapy or in combination with NRTI(s). This overall safety profile remained similar for 107 patients treated with CRIXIVAN monotherapy or in combination with NRTI(s) for up to 48 weeks. Adverse reactions, including nephrolithiasis, may lead to treatment interruption.

In controlled clinical trials conducted world–wide, 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 adult Caucasian males (15 % females).

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

The following adverse reactions have been reported during clinical studies in adults and/or post-marketing use for CRIXIVAN monotherapy and/or CRIXIVAN with combination antiretroviral therapy (CART).

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the

available data). Adverse reactions have also been reported during post-marketing experience* as they are derived from spontaneous reports, incidences cannot be determined.

System Organ Class	Frequency	Adverse reactions CRIXIVAN
Blood and lymphatic system disorders	Very common Not known*	increases in MCV, decreases in neutrophils increased spontaneous bleeding in patients with haemophilia, anemia including acute haemolytic anaemia, thrombocytopenia (see section 4.4).
Immune system disorders	Not known*	anaphylactoid reactions
Metabolism and nutrition disorders	Not known*	new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia.
Nervous system disorders	Very common Common Not known*	headache, dizziness insomnia, hypoaesthesia; paraesthesia oral paraesthesia.
Gastrointestinal disorders	Very common Common Not known*	nausea, vomiting, diarrhoea, dyspepsia flatulence, dry mouth, acid regurgitation hepatitis, including reports of hepatic failure, pancreatitis.
Hepato-biliary disorders	Very Common Not known*	isolated asymptomatic hyperbilirubinaemia, increased ALT and AST liver function abnormalities
Skin and subcutaneous tissue disorders	Very common Common Not known*	rash, dry skin pruritus rash including erythema multiforme and Stevens Johnson syndrome, hypersensitivity vasculitis, alopecia, hyperpigmentation, urticaria; ingrown toenails and/or paronychia.
Musculoskeletal and connective tissue disorders	Common Not known*	myalgia myositis, rhabdomyolysis, increased CPK, osteonecrosis (see section 4.4), periarthritis.

System Organ Class	Frequency	Adverse reactions CRIXIVAN
Renal and urinary disorders	Very common Common Not known*	haematuria, proteinuria, crystalluria nephrolithiasis, dysuria. nephrolithiasis, in some cases with renal insufficiency or acute renal failure; pyelonephritis, interstitial nephritis, sometimes associated with indinavir crystal deposits. In some patients, resolution of the interstitial nephritis did not occur following discontinuation of indinavir therapy; renal insufficiency, renal failure, leucocyturia (see section 4.4).
General disorders and administration site conditions	Very common	asthenia/fatigue, taste perversion, abdominal pain.

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Description of selected adverse reactions
Nephrolithiasis
Nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria), has been reported in approximately 10 % (252/2,577) of patients receiving CRIXIVAN in clinical trials 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).

Hyperbilirubinaemia
Isolated asymptomatic hyperbilirubinaemia (total bilirubin ≥ 2.5 mg/dL, 43 mcmol/L) was reported predominantly as elevated indirect bilirubin and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has occurred in approximately 14 % of patients treated with CRIXIVAN alone or in combination with other antiretroviral agents. Most patients continued treatment with CRIXIVAN without dose reduction and bilirubin values gradually declined toward baseline. Hyperbilirubinaemia occurred more frequently at doses exceeding 2.4 g/day compared to doses less than 2.4 g/day.

Paediatric population
In clinical trials in paediatric patients (≥ 3 years), the adverse reaction profile was similar to that for adult patients except for a higher frequency of nephrolithiasis of 29 % (20/70) in paediatric patients treated with CRIXIVAN. Asymptomatic pyuria of unknown etiology was noted in 10.9 % (6/55) of paediatric patients who received CRIXIVAN. Some of these events were associated with mild elevation of serum creatinine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been reports of human overdose with CRIXIVAN. The most commonly reported symptoms were gastro-intestinal (e.g., nausea, vomiting, diarrhoea) and renal (e.g., nephrolithiasis, flank pain, haematuria).

It is not known whether indinavir is dialyzable by peritoneal or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitor, ATC code J05AE02

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 (IC_{95}) 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 (NNRTIs). 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 NNRTIs.

Medicinal product resistance
Loss of suppression of viral RNA levels occurred in some patients; however, CD4 cell counts were often sustained above pre–treatment 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 amino acid sites in the protease have been associated with indinavir resistance: L10, K20, L24, M46, I54, L63, I64, A71, V82, I84, and L90. The basis for their contributions to resistance, however, is complex. None of these substitutions was either necessary or sufficient for resistance. For example, no single substitution or pair of substitutions was capable of engendering measurable (≥ four–fold) resistance to indinavir, and the level of resistance was dependent on the ways in which multiple substitutions were combined. In general, however, higher levels of resistance resulted from the co–expression of greater numbers of substitutions at the eleven identified positions. Among patients experiencing viral RNA rebound during indinavir monotherapy at 800 mg q8h, substitutions at only three of these sites were observed in the majority of patients: V82 (to A or F), M46 (to I or L), and L10 (to I or R). Other substitutions were observed less frequently. The observed amino acid

substitutions appeared to accumulate sequentially and in no consistent order, probably as a result of ongoing viral replication.

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

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).

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 PIs, 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

Adults

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/mm^3.

In one published study, 20 HIV-infected patients with undetectable plasma viral load (< 200 copies/mL) receiving indinavir 800 mg every 8 hours were switched in an open, cross-over design to indinavir/ritonavir 400/100 mg every 12 hours. Eighteen patients completed the study to week 48. Viral load remained < 200 copies/mL for 48 weeks in all patients.

Another published study evaluated the efficacy and safety of indinavir/ritonavir 400/100 mg every 12 hours in 40 antiretroviral naïve patients. Thirty subjects completed 48 weeks of treatment. At week 4, the indinavir C_{min} was 500 ng/mL with substantial trough variability (range 5 to 8,100 ng/mL). By intent to treat analysis 65 % of patients had HIV RNA < 400 copies/mL and 50 % had viral load < 50 copies/mL; by on-treatment analysis 96 % of patients had HIV RNA < 400 copies/mL and 74 % had viral load < 50 copies/mL.

Eighty antiretroviral naïve patients were entered into a third published study. In this open label non-randomized single arm study, patients were treated with stavudine and lamivudine plus indinavir/ritonavir 400/100 mg every 12 hours. Sixty-two patients completed the study to week 96. In the intent to treat and on treatment analyses the proportion of patients with HIV RNA of < 50 copies/mL was 68.8 % and 88.7 %, respectively, at week 96.

Indinavir alone or in combination with nucleoside analogues (zidovudine/stavudine and lamivudine) has been shown to delay clinical progression rate compared with nucleoside analogues and to provide a sustained effect on viral load and CD4 count.

In zidovudine experienced patients, indinavir, zidovudine and lamivudine in combination compared with lamivudine added to zidovudine reduced the probability of AIDS defining illness or death (ADID) at 48 weeks from 13 % to 7 %. Similarly, in antiretroviral naive patients, indinavir with and without zidovudine compared with zidovudine alone reduced the probability of ADID at 48 weeks

from 15 % with zidovudine alone to approximately 6 % with indinavir alone or in combination with zidovudine.

Effects on viral load were consistently more pronounced in patients treated with indinavir in combination with nucleoside analogues, but the proportion of patients with serum viral RNA below the limit of quantification (500 copies/mL) varied between studies, at week 24 from 40 % to more than 80 %. This proportion tends to remain stable over prolonged periods of follow–up. Similarly, effects on CD4 cell count tend to be more pronounced in patients treated with indinavir in combination with nucleoside analogues compared with indinavir alone. Within studies, this effect is sustained also after prolonged periods of follow–up.

Paediatric population
Two clinical trials in 41 paediatric patients (4 to 15 years of age) were designed to characterise the safety, antiretroviral activity, and pharmacokinetics of indinavir in combination with stavudine and lamivudine. In one study, at week 24, the proportion of patients with plasma viral RNA below 400 copies/mL was 60 %; the mean increase in CD4 cell counts was 242 cells/mm^3; and the mean increase in percent CD4 cell counts was 4.2 %. At week 60, the proportion of patients with plasma viral RNA below 400 copies/mL was 59 %. In another study, at week 16, the proportion of patients with plasma viral RNA below 400 copies/mL was 59 %; the mean increase in CD4 cell counts was 73 cells/mm^3; and the mean increase in percent CD4 cell counts was 1.2 %. At week 24, the proportion of patients with plasma viral RNA below 400 copies/mL was 60 %.

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 1,000–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. The bioavailability of a single 800–mg dose of indinavir was approximately 65 % (90 % CI, 58 – 72 %).

Data from a steady state study in healthy volunteers indicate that there is a diurnal variation in the pharmacokinetics of indinavir. Following a dose regimen of 800 mg every 8 hours, measured peak plasma concentrations (C_{max}) after morning, afternoon and evening doses were 15,550 nM, 8,720 nM and 8,880 nM, respectively. Corresponding plasma concentrations at 8 hours post dose were 220 nM, 210 nM and 370 nM, respectively. The relevance of these findings for ritonavir boosted indinavir is unknown. At steady state following a dose regimen of 800 mg every 8 hours, HIV–seropositive adult patients in one study achieved geometric means of: $AUC_{0\text{-}8h}$ of 27,813 nM*h (90 % confidence interval = 22,185, 34,869), peak plasma concentrations 11,144 nM (90 % confidence interval = 9,192, 13,512) and plasma concentrations at 8 hours post dose 211 nM (90 % confidence interval = 163,274).

Food effect
At steady state following a dose regimen of 800 mg/100 mg of indinavir/ritonavir every 12 hours with a low-fat meal, healthy volunteers in one study achieved geometric means: $AUC_{0\text{-}12h}$ 116,067 nM*h (90 % confidence interval = 101,680, 132,490), peak plasma concentrations 19,001 nM (90 % confidence interval = 17,538, 20,588), and plasma concentrations at 12 hours post dose 2,274 nM (90 % confidence interval = 1,701, 3,042). No significant difference in exposure was seen when the regimen was given with a high-fat meal.

Indinavir boosted regimen. Limited data are available on the pharmacokinetics of indinavir in association with low dose ritonavir. The pharmacokinetics of indinavir (400 mg) with ritonavir (100 mg) dosed twice daily was examined in two studies. Pharmacokinetic analysis in one study was performed on nineteen of the patients, with a median (range) indinavir AUC 0-12hr, Cmax, and Cmin

of 25,421 nM*h (21,489 – 36,236 nM*h), 5,758 nM (5,056 – 6,742 nM) and 239 (169 – 421 nM), respectively. The pharmacokinetic parameters in the second study were comparable.

In HIV–infected paediatric patients, a dose regimen of indinavir hard capsules, 500 mg/m^2 every 8 hours, produced $AUC_{0–8hr}$ values of 27,412 nM*h, peak plasma concentrations of 12,182 nM, and plasma concentrations at 8 hours post dose of 122 nM. The AUC and peak plasma concentrations were generally similar to those previously observed in HIV–infected adults receiving the recommended dose of 800 mg every 8 hours; it should be observed that the plasma concentrations 8 hours post dose were lower.

During pregnancy, it has been demonstrated that the systemic exposure of indinavir is relevantly decreased (PACTG 358. Crixivan, 800 mg every 8 hours + zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day). The mean indinavir plasma AUC_{0-8hr} at week 30-32 of gestation (n = 11) was 9,231 nM∗hr, which is 74 % (95 % CI: 50 %, 86 %) lower than that observed 6 weeks postpartum. Six of these 11 (55 %) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in non-pregnant patients in another study (see section 4.6).

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.

The pharmacokinetics of indinavir taken as indinavir sulphate salt (from opened hard capsules) mixed in apple sauce were generally comparable to the pharmacokinetics of indinavir taken as hard capsules, under fasting conditions. In HIV–infected paediatric patients, the pharmacokinetic parameters of indinavir in apple sauce were: $AUC_{0–8hr}$ of 26,980 nM*h; peak plasma concentration of 13,711 nM; and plasma concentration at 8 hours post dose of 146 nM.

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 proteinase inhibitory activity.

Elimination
Over the 200–1,000–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 medicinal product following single dose administration in the fasted state was 10.4 % following a 700–mg dose, and 12.0 % following a 1,000–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 race.

There are no clinically significant differences in the pharmacokinetics of indinavir in HIV seropositive women compared to HIV seropositive men.

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.

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 medicinal product –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 5,000 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
No carcinogenicity was noted in mice at the maximum tolerated dose, which corresponded to a systemic exposure approximately 2 to 3 times higher than the clinical exposure. In rats, at similar exposure levels, an increased incidence of thyroid adenomas was seen, probably related to an increase in release of thyroid stimulating hormone secondary to an increase in thyroxine clearance. The relevance of the findings to humans is likely limited.

Developmental Toxicity
Developmental toxicity studies were performed in rats, rabbits and dogs (at doses which produced systemic exposures comparable to or slightly greater than human exposure) and revealed no evidence of teratogenicity. No external or visceral changes were observed in rats, however, increases in the incidence of supernumerary ribs and of cervical ribs were seen. No external, visceral, or skeletal changes were observed in rabbits or dogs. In rats and rabbits, no effects on embryonic/foetal survival or foetal weights were observed. In dogs, a slight increase in resorptions was seen; however, all foetuses in medication-treated animals were viable, and the incidence of live foetuses in medication-treated animals was comparable to that in controls.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
anhydrous lactose
magnesium stearate

Capsule shell:
gelatin
titanium dioxide (E 171)

printing ink: titanium dioxide (E 171), indigo carmine (E 132) and iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years for HDPE bottles containing 90 and 180 hard capsules.

6.4 Special precautions for storage

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with a polypropylene cap and a foil induction cap containing 90 or 180 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The bottles contain desiccant canisters that should remain in the container.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/004
EU/1/96/024/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 October 1996
Date of latest renewal: 18 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CRIXIVAN 200 mg – packs of 180, 270 and 360 capsules – Outer carton

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 200 mg hard capsules
Indinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains indinavir sulphate corresponding to 200 mg of indinavir.

3. LIST OF EXCIPIENTS

Anhydrous lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules
270 hard capsules
360 hard capsules

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Hard capsules should be swallowed whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Desiccant should not be removed from the container.
Desiccant should not be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS:

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/001 180 hard capsules
EU/1/96/024/002 270 hard capsules
EU/1/96/024/003 360 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRIXIVAN 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CRIXIVAN 200 mg – packs of 180, 270 and 360 capsules – Bottle label

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 200 mg hard capsules
Indinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains indinavir sulphate corresponding to 200 mg of indinavir.

3. LIST OF EXCIPIENTS

Anhydrous lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules
270 hard capsules
360 hard capsules

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Hard capsules should be swallowed whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Desiccant should not be removed from the container.
Desiccant should not be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS:

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/001 180 hard capsules
EU/1/96/024/002 270 hard capsules
EU/1/96/024/003 360 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CRIXIVAN 400 mg – packs of 90 and 180 capsules – Outer carton

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 400 mg hard capsules
Indinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.

3. LIST OF EXCIPIENTS

Anhydrous lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules
180 hard capsules

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Hard capsules should be swallowed whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Desiccant should not be removed from the container.
Desiccant should not be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS:

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/004 90 hard capsules
EU/1/96/024/005 180 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRIXIVAN 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CRIXIVAN 400 mg – packs of 90 and 180 capsules – Bottle label

1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 400 mg hard capsules
Indinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.

3. LIST OF EXCIPIENTS

Anhydrous lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules
180 hard capsules

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Hard capsules should be swallowed whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Desiccant should not be removed from the container.
Desiccant should not be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS:

Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/004 90 hard capsules
EU/1/96/024/005 180 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CRIXIVAN 200 mg hard capsules
indinavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CRIXIVAN is and what it is used for

What CRIXIVAN is
CRIXIVAN contains a substance called indinavir. It belongs to a group of medicines called 'protease inhibitors'.

What CRIXIVAN is used for
CRIXIVAN is used to treat Human Immunodeficiency Virus (HIV) in adults. CRIXIVAN is used at the same time as other HIV treatments (antiretroviral medicines). This is called combination antiretroviral therapy.
- An example of another medicine that might be given to you, at the same time as CRIXIVAN, is ritonavir.

How CRIXIVAN works
CRIXIVAN treats HIV and helps to lower the number of HIV particles in your blood.

CRIXIVAN helps to:
- lower the risk that you get illnesses related to HIV
- lower the amount of HIV in your body (your 'viral load')
- raise your CD4 (T) cell count. CD4 cells are an important part of your immune system. The main role of the immune system is to protect you from infections.

CRIXIVAN may not do these things in all patients. Your doctor will monitor how this medicine works for you.

2. What you need to know before you take CRIXIVAN

Do not take CRIXIVAN:
- if you are allergic to indinavir or any of the other ingredients of this medicine (listed in Section 6).
- if you are taking any of the following medicines:

- rifampicin - an antibiotic used to treat infections
- cisapride - used for gut problems
- amiodarone - used for heart rhythm problems
- pimozide - used for some mental health problems
- lovastatin or simvastatin - used to lower cholesterol
- St. John's wort (*Hypericum perforatum*) - a herbal medicine used for depression
- ergot tartramine (with or without caffeine) - used for migraines
- astemizole or terfenadine - antihistamines used for hay fever and other allergies
- quetiapine – used for some mental illnesses such as schizophrenia, bipolar disorder and major depressive disorder
- alprazolam, triazolam and midazolam (by mouth) - used to make you calmer or help you sleep.

Do not take CRIXIVAN if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

In addition, when CRIXIVAN is given at the same time as the medicine ritonavir:
Do not take either CRIXIVAN or ritonavir:

- if you have liver problems
- if you are taking any of the following medicines:
  - fusidic acid - an antibiotic used to treat infections
  - piroxicam - used for arthritis
  - alfuzosin - used for prostate problems
  - bepridil - used for chest pain (angina)
  - clozapine - used for some mental health problems
  - pethidine or propoxyphene - used for pain
  - estazolam or flurazepam - used to help you sleep
  - clorazepate or diazepam - used to make you calmer
  - encainide, flecanide, propafenone, or quinidine - used for uneven heartbeat problems.

Do not take either CRIXIVAN or ritonavir if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking CRIXIVAN if you have had or develop any of the following:

- **allergies**

- **kidney problems** (including inflammation of the kidneys, kidney stones, or back pain with or without blood in your urine)

- **'haemophilia'** – CRIXIVAN may make you more likely to bleed. If you notice bleeding or if you feel weak, talk to your doctor straight away.

- **liver problems** – people with 'chronic hepatitis B or C' or 'cirrhosis' who are treated with 'antiretroviral' medicines are more likely to have serious and potentially fatal liver side effects with this medicine. You may need to have blood tests to check how your liver is working.

- **severe pain, tenderness or weakness in your muscles** – this is more likely to happen if you are taking cholesterol-lowering medicines called 'statins' (such as simvastatin). On rare occasions the muscle problems can be serious (rhabdomyolysis). Inform your doctor as soon as possible if you develop severe muscle pain or weakness.

- **signs of infection** – this may be a previous infection which comes back soon after anti-HIV treatment is started. This may be because the body is able to start fighting infections again. This happens in some people with advanced HIV infection (AIDS) and who have had HIV related infections before. If you notice any symptoms of infection, please inform your doctor immediately.

- **autoimmune disorders** (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **bone problems** – signs include stiff joints, aches and pains, especially the hip and difficulty moving. If you notice any of these signs, talk to your doctor. Such problems might be due to a bone disease called 'osteonecrosis' (loss of blood supply to the bone causing bone death), which can occur months to years after starting HIV therapy. The risk of you having bone problems is higher if you:
  - drink alcohol
  - have a high body mass index
  - have an immune system that is very weak
  - have been taking corticosteroids at the same time as CRIXIVAN
  - take combination antiretroviral therapy for a long time.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

Children and adolescents
CRIXIVAN is not recommended in children under the age of 18 years.

Other medicines and CRIXIVAN
Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

CRIXIVAN can affect the way some other medicines work. Also some other medicines can affect the way CRIXIVAN works.

Ritonavir
Ritonavir is used for increasing the blood levels of CRIXIVAN or, less frequently and then at higher doses, for HIV treatment. Talk to your doctor if you are going to take both CRIXIVAN and ritonavir. Also look at the Package Leaflet for ritonavir.

Please see **'Do not take CRIXIVAN'** and **'Do not take either CRIXIVAN or ritonavir'** above under Section 2 for an important list of medicines that you must not combine with CRIXIVAN. Do not take CRIXIVAN if you are taking or have recently taken any of these medicines. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

In addition, talk to your doctor, pharmacist or nurse before taking CRIXIVAN if you are taking any of the following medicines since your doctor may want to adjust the dose of your medicines:
- theophylline - used for asthma
- warfarin - used to thin the blood
- morphine, fentanyl - used for pain
- buspirone - used to make you calmer
- fluconazole - used for fungal infections

- venlafaxine, trazodone - used for depression
- tacrolimus, ciclosporin - used mainly after organ transplantation
- delavirdine, efavirenz, nevirapine - used for HIV
- amprenavir, saquinavir, atazanavir - used for HIV
- sildenafil, vardenafil, tadalafil - used for impotence
- dexamethasone - used to stop swelling (inflammation)
- itraconazole, ketoconazole - used to treat fungal infections
- atorvastatin, rosuvastatin, pravastatin, fluvastatin - used to lower cholesterol
- fexofenadine, loratidine - antihistamines used for hay fever and other allergic conditions
- oral contraceptive medicines ('The Pill') containing norethindrone or ethinyl estradiol
- phenobarbital, phenytoin, carbamazepine, divalproex, lamotrigine - medicines used to treat fits (epilepsy)
- midazolam (by injection) - used for acute fits (seizures) and to send patients to sleep before some medical procedures
- amlodipine, felodipine, nifedipine, nicardipine, digoxin, diltiazem - used for high blood pressure and some heart problems.
- quetiapine – used for some mental illnesses such as schizophrenia, bipolar disorder and major depressive disorder

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

CRIXIVAN with food and drink
See Section 3 below for information on how to take CRIXIVAN. It is however especially important that you:

- do not take CRIXIVAN with food that is high in calories, fat and protein. This is because these foods stop your body being able to take in as much CRIXIVAN and it will not work as well.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, only take CRIXIVAN if your doctor decides it is clearly necessary. It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman.

- It is recommended that women with HIV do not breast-feed. This is to stop HIV being passed on to their baby.

Driving and using machines
Dizziness and blurred vision have been reported during treatment with CRIXIVAN. If this happens, do not drive or operate machines.

Other things you should know
CRIXIVAN is not a cure for HIV. You may still get infections or other illnesses related to HIV. So you still need to keep seeing your doctor while you are taking CRIXIVAN.

HIV is spread by blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

CRIXIVAN contains lactose
This medicine contains lactose (type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3. How to take CRIXIVAN

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

The recommended dose of CRIXIVAN is:
- Four 200 mg capsules (800 mg) - taken three times a day (every 8 hours).
  This means you will take a total of twelve 200 mg capsules (2400 mg) each day.

You usually take less CRIXIVAN if you are also taking ritonavir. The recommended doses are:
- CRIXIVAN - two 200 mg capsules (400 mg) - taken twice a day.
  This means you will take a total of four 200 mg capsules (800 mg) each day.
- ritonavir - 100 mg - taken twice a day.

Taking this medicine
- Take this medicine by mouth.
- Swallow the capsules whole with a drink of water, skimmed or low fat milk, juice, tea or coffee.
- Do not crush or chew the capsules.
- It is important for adults to drink at least 1.5 litres of liquid each day while taking CRIXIVAN. This will help lower the risk of you getting kidney stones.
- Do not take CRIXIVAN with food that is high in calories, fat and protein. This is because these stop your body being able to take in as much CRIXIVAN and it will not work as well.

When to take
- Take 1 hour before or 2 hours after a meal.
- If you cannot take it without food then take CRIXIVAN with a low-fat light meal. This could be dry toast with jam or cornflakes with skimmed or low-fat milk and sugar.
- If you are also taking ritonavir, then you can take CRIXIVAN at any time of the day with or without food.

If you take more CRIXIVAN than you should
If you take more CRIXIVAN than you should, talk to your doctor as soon as possible. The following effects may happen:
- nausea
- vomiting
- diarrhoea
- back pain
- blood in your urine.

If you forget to take CRIXIVAN
Do not take a double dose to make up for a forgotten dose. If you have missed a dose, do not take it later in the day. Simply continue to follow your usual schedule.

If you stop taking CRIXIVAN
It is important that you take CRIXIVAN exactly as your doctor tells you to - he or she will tell you how long you should take your medicine.
- Do not stop taking CRIXIVAN without talking to your doctor.
- This is because reducing or missing doses will make it more likely that HIV will become resistant to CRIXIVAN.
- If this happens, your treatment will stop working.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported by patients taking CRIXIVAN:

See your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- allergic reactions - signs include itchy skin, redness of the skin, 'wheals' or 'hives', swelling of the face, lips, tongue or throat and difficulty breathing. It is not known how often this may happen (cannot be estimated from the available data), but the reaction can sometimes be severe and include shock

There are also other side effects that you may get while taking this medicine such as increased bleeding in haemophiliacs, muscle problems, signs of infection, and bone problems. Please see 'Warnings and precautions' in Section 2 above.

Additional side effects include:

Very common (affects more than 1 in 10 people):

- headache
- rash or dry skin
- nausea
- vomiting
- altered taste sensations
- indigestion or diarrhoea
- stomach pain or swelling
- feeling dizzy, weak or tired.

Common (affects less than 1 in 10 people):

- passing gas
- itching
- dry mouth
- acid reflux
- muscle pain
- pain on urination
- difficulty getting to sleep
- feeling numb or unusual feeling of the skin.

The following side effects have also been reported since the medicine has been used. How often they happen is not known:

- hair loss
- inflamed pancreas
- severe skin reactions
- darkening skin colour
- having a numb mouth
- low red blood cell count
- ingrown toenails with or without infection

- liver problems such as inflammation or liver failure
- kidney problems such as kidney infection, worsening or loss of kidney function
- pain and difficulty moving shoulder.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CRIXIVAN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle or carton after 'EXP'. The expiry date refers to the last day of that month.

Store CRIXIVAN in the original bottle and keep the bottle tightly closed to protect it from moisture. The bottle contains desiccant canisters that should remain in the bottle.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What CRIXIVAN contains

- The active substance is indinavir. Each hard capsule contains indinavir sulphate corresponding to 200 mg of indinavir.
- The other ingredients are anhydrous lactose, magnesium stearate, gelatin and titanium dioxide (E 171).
- The capsules are printed with printing ink containing indigo carmine (E 132).

What CRIXIVAN looks like and contents of the pack

CRIXIVAN 200 mg hard capsules are supplied in HDPE bottles with a polypropylene cap and a foil seal containing 180, 270 or 360 capsules. Not all pack sizes may be marketed.

The capsules are semi-translucent white and coded 'CRIXIVAN 200 mg' on them in blue.

Marketing Authorisation Holder and Manufacturer

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Manufacturer: Merck Sharp & Dohme B.V., Waarderweg 39**,** Postbus 581**,** 2003 PC Haarlem
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Package leaflet: Information for the user

CRIXIVAN 400 mg hard capsules
indinavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CRIXIVAN is and what it is used for

What CRIXIVAN is
CRIXIVAN contains a substance called indinavir. It belongs to a group of medicines called 'protease inhibitors'.

What CRIXIVAN is used for
CRIXIVAN is used to treat Human Immunodeficiency Virus (HIV) in adults. CRIXIVAN is used at the same time as other HIV treatments (antiretroviral medicines). This is called combination antiretroviral therapy.
- An example of another medicine that might be given to you, at the same time as CRIXIVAN, is ritonavir.

How CRIXIVAN works
CRIXIVAN treats HIV and helps to lower the number of HIV particles in your blood.

CRIXIVAN helps to:
- lower the risk that you get illnesses related to HIV
- lower the amount of HIV in your body (your 'viral load')
- raise your CD4 (T) cell count. CD4 cells are an important part of your immune system. The main role of the immune system is to protect you from infections.

CRIXIVAN may not do these things in all patients. Your doctor will monitor how this medicine works for you.

2. What you need to know before you take CRIXIVAN

Do not take CRIXIVAN:
- if you are allergic to indinavir or any of the other ingredients of this medicine (listed in Section 6).
- if you are taking any of the following medicines:

- rifampicin - an antibiotic used to treat infections
- cisapride - used for gut problems
- amiodarone - used for heart rhythm problems
- pimozide - used for some mental health problems
- lovastatin or simvastatin - used to lower cholesterol
- St. John's wort (*Hypericum perforatum*) - a herbal medicine used for depression
- ergot tartramine (with or without caffeine) - used for migraines
- astemizole or terfenadine - antihistamines used for hay fever and other allergies
- quetiapine – used for some mental illnesses such as schizophrenia, bipolar disorder and major depressive disorder
- alprazolam, triazolam and midazolam (by mouth) - used to make you calmer or help you sleep.

Do not take CRIXIVAN if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

In addition, when CRIXIVAN is given at the same time as the medicine ritonavir:
Do not take either CRIXIVAN or ritonavir:
- if you have liver problems
- if you are taking any of the following medicines:
  - fusidic acid - an antibiotic used to treat infections
  - piroxicam - used for arthritis
  - alfuzosin - used for prostate problems
  - bepridil - used for chest pain (angina)
  - clozapine - used for some mental health problems
  - pethidine or propoxyphene - used for pain
  - estazolam or flurazepam - used to help you sleep
  - clorazepate or diazepam - used to make you calmer
  - encainide, flecanide, propafenone, or quinidine - used for uneven heartbeat problems.

Do not take either CRIXIVAN or ritonavir if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking CRIXIVAN if you have had or develop any of the following:

- **allergies**

- **kidney problems** (including inflammation of the kidneys, kidney stones, or back pain with or without blood in your urine)

- **'haemophilia'** – CRIXIVAN may make you more likely to bleed. If you notice bleeding or if you feel weak, talk to your doctor straight away.

- **liver problems** – people with 'chronic hepatitis B or C' or 'cirrhosis' who are treated with 'antiretroviral' medicines are more likely to have serious and potentially fatal liver side effects with this medicine. You may need to have blood tests to check how your liver is working.

- **severe pain, tenderness or weakness in your muscles** – this is more likely to happen if you are taking cholesterol-lowering medicines called 'statins' (such as simvastatin). On rare occasions the muscle problems can be serious (rhabdomyolysis). Inform your doctor as soon as possible if you develop severe muscle pain or weakness.

- **signs of infection** – this may be a previous infection which comes back soon after anti-HIV treatment is started. This may be because the body is able to start fighting infections again. This happens in some people with advanced HIV infection (AIDS) and who have had HIV related infections before. If you notice any symptoms of infection, please inform your doctor immediately.

- **autoimmune disorders** (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **bone problems** – signs include stiff joints, aches and pains, especially of the hip and difficulty moving. If you notice any of these signs, talk to your doctor. Such problems might be due to a bone disease called 'osteonecrosis' (loss of blood supply to the bone causing bone death), which can occur months to years after starting HIV therapy. The risk of you having bone problems is higher if you:
  - drink alcohol
  - have a high body mass index
  - have an immune system that is very weak
  - have been taking corticosteroids at the same time as CRIXIVAN
  - take combination antiretroviral therapy for a long time.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

Children and adolescents
CRIXIVAN is not recommended in children under the age of 18 years.

Other medicines and CRIXIVAN
Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

CRIXIVAN can affect the way some other medicines work. Also some other medicines can affect the way CRIXIVAN works.

Ritonavir
Ritonavir is used for increasing the blood levels of CRIXIVAN or, less frequently and then at higher doses, for HIV treatment. Talk to your doctor if you are going to take both CRIXIVAN and ritonavir. Also look at the Package Leaflet for ritonavir.

Please see **'Do not take CRIXIVAN'** and **'Do not take either CRIXIVAN or ritonavir'** above under Section 2 for an important list of medicines that you must not combine with CRIXIVAN. Do not take CRIXIVAN if you are taking or have recently taken any of these medicines. If you are not sure, talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

In addition, talk to your doctor, pharmacist or nurse before taking CRIXIVAN if you are taking any of the following medicines since your doctor may want to adjust the dose of your medicines:

- theophylline - used for asthma
- warfarin - used to thin the blood
- morphine, fentanyl - used for pain
- buspirone - used to make you calmer
- fluconazole - used for fungal infections

- venlafaxine, trazodone - used for depression
- tacrolimus, ciclosporin - used mainly after organ transplantation
- delavirdine, efavirenz, nevirapine - used for HIV
- amprenavir, saquinavir, atazanavir - used for HIV
- sildenafil, vardenafil, tadalafil - used for impotence
- dexamethasone - used to stop swelling (inflammation)
- itraconazole, ketoconazole - used to treat fungal infections
- atorvastatin, rosuvastatin, pravastatin, fluvastatin - used to lower cholesterol
- fexofenadine, loratidine - antihistamines used for hay fever and other allergic conditions
- oral contraceptive medicines ('The Pill') containing norethindrone or ethinyl estradiol
- phenobarbital, phenytoin, carbamazepine, divalproex, lamotrigine - medicines used to treat fits (epilepsy)
- midazolam (by injection) - used for acute fits (seizures) and to send patients to sleep before some medical procedures
- amlodipine, felodipine, nifedipine, nicardipine, digoxin, diltiazem - used for high blood pressure and some heart problems.
- quetiapine – used for some mental illnesses such as schizophrenia, bipolar disorder and major depressive disorder

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking CRIXIVAN.

CRIXIVAN with food and drink
See Section 3 below for information on how to take CRIXIVAN. It is however especially important that you:

- do not take CRIXIVAN with food that is high in calories, fat and protein. This is because these foods stop your body being able to take in as much CRIXIVAN and it will not work as well.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, only take CRIXIVAN if your doctor decides it is clearly necessary. It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman.

- It is recommended that women with HIV do not breast-feed. This is to stop HIV being passed on to their baby.

Driving and using machines
Dizziness and blurred vision have been reported during treatment with CRIXIVAN. If this happens, do not drive or operate machines.

Other things you should know
CRIXIVAN is not a cure for HIV. You may still get infections or other illnesses related to HIV. So you still need to keep seeing your doctor while you are taking CRIXIVAN.

HIV is spread by blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

CRIXIVAN contains lactose
This medicine contains lactose (type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3. How to take CRIXIVAN

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

The recommended dose of CRIXIVAN is:
- Two 400 mg capsules (800 mg) - taken three times a day (every 8 hours).
  This means you will take a total of six 400 mg capsules (2400 mg) each day.

You usually take less CRIXIVAN if you are also taking ritonavir. The recommended doses are:
- CRIXIVAN – one 400 mg capsules (400 mg) - taken twice a day.
  This means you will take a total of two 400 mg capsules (800 mg) each day.
- ritonavir - 100 mg - taken twice a day.

Taking this medicine
- Take this medicine by mouth.
- Swallow the capsules whole with a drink of water, skimmed or low fat milk, juice, tea or coffee.
- Do not crush or chew the capsules.
- It is important for adults to drink at least 1.5 litres of liquid each day while taking CRIXIVAN. This will help lower the risk of you getting kidney stones.
- Do not take CRIXIVAN with food that is high in calories, fat and protein. This is because these stop your body being able to take in as much CRIXIVAN and it will not work as well.

When to take
- Take 1 hour before or 2 hours after a meal.
- If you cannot take it without food then take CRIXIVAN with a low-fat light meal. This could be dry toast with jam or cornflakes with skimmed or low-fat milk and sugar.
- If you are also taking ritonavir, then you can take CRIXIVAN at any time of the day with or without food.

If you take more CRIXIVAN than you should
If you take more CRIXIVAN than you should, talk to your doctor as soon as possible. The following effects may happen:
- nausea
- vomiting
- diarrhoea
- back pain
- blood in your urine.

If you forget to take CRIXIVAN
Do not take a double dose to make up for a forgotten dose. If you have missed a dose, do not take it later in the day. Simply continue to follow your usual schedule.

If you stop taking CRIXIVAN
It is important that you take CRIXIVAN exactly as your doctor tells you to - he or she will tell you how long you should take your medicine.
- Do not stop taking CRIXIVAN without talking to your doctor.
- This is because reducing or missing doses will make it more likely that HIV will become resistant to CRIXIVAN.
- If this happens, your treatment will stop working.

If you have any further questions on the use of thismedicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported by patients taking CRIXIVAN:

See your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- allergic reactions - signs include itchy skin, redness of the skin, 'wheals' or 'hives', swelling of the face, lips, tongue or throat and difficulty breathing. It is not known how often this may happen (cannot be estimated from the available data), but the reaction can sometimes be severe and include shock

There are also other side effects that you may get while taking this medicine such as increased bleeding in haemophiliacs, muscle problems, signs of infection, and bone problems. Please see 'Warnings and precautions' in Section 2 above.

Additional side effects include:

Very common (affects more than 1 in 10 people):

- headache
- rash or dry skin
- nausea
- vomiting
- altered taste sensations
- indigestion or diarrhoea
- stomach pain or swelling
- feeling dizzy, weak or tired.

Common (affects less than 1 in 10 people):

- passing gas
- itching
- dry mouth
- acid reflux
- muscle pain
- pain on urination
- difficulty getting to sleep
- feeling numb or unusual feeling of the skin.

The following side effects have also been reported since the medicine has been used. How often they happen is not known:

- hair loss
- inflamed pancreas
- severe skin reactions
- darkening skin colour
- having a numb mouth
- low red blood cell count
- ingrown toenails with or without infection

- liver problems such as inflammation or liver failure
- kidney problems such as kidney infection, worsening or loss of kidney function
- pain and difficulty moving shoulder.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CRIXIVAN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle or carton after 'EXP'. The expiry date refers to the last day of that month.

Store CRIXIVAN in the original bottle and keep the bottle tightly closed to protect it from moisture. The bottle contains desiccant canisters that should remain in the bottle.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What CRIXIVAN contains

- The active substance is indinavir. Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.
- The other ingredients are anhydrous lactose, magnesium stearate, gelatin and titanium dioxide (E 171).
- The capsules are printed with printing ink containing titanium dioxide (E 171), indigo carmine (E 132) and iron oxide (E 172).

What CRIXIVAN looks like and contents of the pack

CRIXIVAN 400 mg hard capsules are supplied in HDPE bottles with a polypropylene cap and a foil seal containing 90 or 180 capsules. Not all pack sizes may be marketed.

The capsules are semi-translucent white and coded 'CRIXIVAN 400 mg' on them in green.

Marketing Authorisation Holder and Manufacturer

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Other sources of information
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