ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
CRIXIVAN 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains indinavir sulphate corresponding to 100 mg of indinavir.
Excipient: Each 100 mg capsule contains 37.4 mg lactose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsule.
The capsules are semi–translucent white and coded CRIXIVAN™ 100 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, adolescents, and children 4 years of age and older. In adolescents and children, the benefit of indinavir therapy versus the increased risk of nephrolithiasis should particularly be considered (see section 4.4).

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).

Adults
The recommended dosage of CRIXIVAN 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).

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

Children and adolescents (4 to 17 years of age)
The recommended dosage of CRIXIVAN for patients 4 to 17 years of age is 500 mg/m² (dose adjusted from calculated body surface area [BSA] based on height and weight) orally every 8 hours (see table below). This dose should not exceed the equivalent of the adult dose of 800 mg every 8 hours. CRIXIVAN hard capsules should only be given to children who are able to swallow hard capsules. CRIXIVAN has not been studied in children under the age of 4 years (see section 5.1 and 5.2).
Paediatric dose (500 mg/m²) to be administered every 8 hours

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>CRIXIVAN dose Every 8 hours (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>300</td>
</tr>
<tr>
<td>0.75</td>
<td>400</td>
</tr>
<tr>
<td>1.00</td>
<td>500</td>
</tr>
<tr>
<td>1.25</td>
<td>600</td>
</tr>
<tr>
<td>1.50</td>
<td>800</td>
</tr>
</tbody>
</table>

General administration recommendations
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.

To ensure adequate hydration, it is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours. It is also recommended that children who weigh less than 20 kg drink at least 75 ml/kg/day and that children who weigh 20 to 40 kg drink at least 50 ml/kg/day.

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 (see section 4.4).

Special dosing considerations in adults
A dosage reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering itraconazole or ketoconazole concurrently (see section 4.5).

In patients with mild–to–moderate hepatic impairment due to cirrhosis, the dosage of CRIXIVAN 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).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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, 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 should not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encaïnide, flecainide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Ritonavir should not be given with indinavir 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 and paediatric patients. The frequency of nephrolithiasis is higher in paediatric patients than in adult patients. 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. Paediatric patients who experience flank pain should be evaluated for the possibility of nephrolithiasis. Evaluation may consist of urinalysis, serum BUN and creatinine, and ultrasound of the bladder and kidneys. The long–term effects of nephrolithiasis in paediatric patients are unknown. Adequate hydration is recommended in all patients on indinavir (see section 4.2 and 4.8).

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 such as children, 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 effects.

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).
**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.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors (PIs). In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

**Fat redistribution**
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

The safety and efficacy of indinavir/ritonavir has not been established in patients with significant underlying liver disorders and should not be used in this patient population.

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.

**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 dosage 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 drug 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). This quantity is not likely to induce symptoms of lactose intolerance (milk intolerance).

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
Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

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 CRIXIVAN and ritonavir 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, 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.

Drugs 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 – UNBOOSTED INDINAVIR

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").

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>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.</td>
<td>Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach.</td>
</tr>
<tr>
<td>Didanosine enteric-coated 400 mg SD (Indinavir 800 mg SD)</td>
<td>Indinavir: ↔ (Relative to Indinavir 800 mg SD alone) Didanosine: ↑</td>
<td>Can be administered without any restrictions with respect to time of administration or food.</td>
</tr>
<tr>
<td>Stavudine 40 mg BID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 800 mg TID alone) Stavudine AUC: ↑ 21 % Stavudine C&lt;sub&gt;min&lt;/sub&gt;: not evaluated</td>
<td>Indinavir and NRTIs can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Zidovudine 200 mg TID (Indinavir 1,000 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 1,000 mg TID alone) Zidovudine AUC: ↑ 39 % Zidovudine C&lt;sub&gt;min&lt;/sub&gt;: ↑ 51 %</td>
<td></td>
</tr>
<tr>
<td>Zidovudine/Lamivudine 200/150 mg TID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 800 mg TID alone) Zidovudine AUC: ↑ 39 % Zidovudine C&lt;sub&gt;min&lt;/sub&gt;: ↑ 51 % Lamivudine AUC: ↔ Lamivudine C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td></td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Delavirdine 400 mg TID (Indinavir 600 mg TID) | Indinavir AUC: ↑ 53 %  
Indinavir C<sub>min</sub> ↑ 298 %  
(Relative to Indinavir 800 mg TID alone)  
Delavirdine: ↔ | Dose reduction of CRIXIVAN to 400-600 mg every 8 hours should be considered. |
| Delavirdine 400 mg TID Indinavir 400 mg TID | Indinavir AUC: ↔  
Indinavir C<sub>min</sub>: ↑ 118 %  
(Relative to Indinavir 800 mg TID alone)  
Delavirdine: ↔ |                                               |
| Efavirenz 600 mg QD (Indinavir 1,000 mg TID) | Indinavir AUC: ↓ 46 %  
Indinavir C<sub>min</sub>: ↓ 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.  
Efavirenz AUC: ↔ | No specific dose recommendation can be given. |
| Efavirenz 200 mg QD (Indinavir 800 mg TID) | Indinavir AUC: ↓ 31 %  
Indinavir C<sub>min</sub>: ↓ 40 %  
Efavirenz AUC: ↔ |                                               |
| 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. |
<p>| 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). |</p>
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| **Ritonavir 100 mg BID** *(Indinavir 800 mg BID)* | Indinavir AUC\(_{24h}\): ↑ 178 %  
Indinavir C\(_{\text{min}}\): ↑ 111-fold;  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC: ↑ 72 %  
Ritonavir C\(_{\text{min}}\): ↑ 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\(_{24h}\): ↓ 1266 %  
Indinavir C\(_{\text{min}}\): ↓ 24-fold;  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC: ↑ 96 %  
Ritonavir C\(_{\text{min}}\): ↑ 371 % | |
| **Ritonavir 400 mg BID** *(Indinavir 800 mg BID)* | Indinavir AUC\(_{24h}\): ↓ 2220 %  
Indinavir C\(_{\text{min}}\): ↓ 24-fold  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC\(_{24h}\): ↔ | |
| **Ritonavir 400 mg BID** *(Indinavir 400 mg BID)* | Indinavir AUC\(_{24h}\): ↓ 168 %  
Indinavir C\(_{\text{min}}\): ↑ 10-fold  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC\(_{24h}\): ↔ | |
| **Ritonavir 100 mg BID** *(Indinavir 400 mg BID)* | Indinavir AUC and C\(_{\text{min}}\): ↔  
(Relative to Indinavir 800 mg TID alone*) | |
| *historical controls* | | |
| **Saquinavir 600 mg SD (hard gel capsule formulation)** *(Indinavir 800 mg TID)* | Saquinavir AUC: ↑ 500 %  
Saquinavir C\(_{\text{min}}\): ↑ 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\(_{\text{min}}\): ↑ 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\(_{\text{min}}\): ↑ 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 |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphamethoxazole/Trimethoprim 800 mg/160 mg BID (Indinavir 400 mg QID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 400 mg QID alone) Sulphamethoxazole AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and sulphamethoxazole/trimethoprim can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole 400 mg QD (Indinavir 1,000 mg TID)</td>
<td>Indinavir AUC: ↓ 24 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 1,000 mg TID alone)</td>
<td>Indinavir and fluconazole can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Itraconazole 200 mg BID (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 49 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended with administering itraconazole concurrently.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: ↓ 20 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 29 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 400 mg TID)</td>
<td>Indinavir AUC: ↓ 56 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 27 % (Relative to Indinavir 800 mg TID alone)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 800 mg TID alone) Isoniazid AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and isoniazid can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Rifabutin 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 34 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 39 % (Relative to Indinavir 800 mg TID alone)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifabutin 150 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 32 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 40 % (Relative to Indinavir 800 mg TID alone)</td>
<td></td>
</tr>
<tr>
<td>Rifampicin 600 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 92 % (Relative to Indinavir 800 mg TID alone) This effect is due to an induction of CYP3A4 by rifampicin.</td>
<td>The use of rifampicin with indinavir is contraindicated.</td>
</tr>
</tbody>
</table>
## Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>

### ANALGESICS

| Methadone 20-60 mg QD (Indinavir 800 mg TID) | Indinavir AUC: ↔ (Relative to Indinavir 800 mg TID historical controls) Methadone AUC and C<sub>min</sub>: ↔ | Indinavir and methadone can be co-administered without dose adjustment. |

### ANTIARRHYTHMICS

| Quinidine 200 mg SD (Indinavir 400 mg SD) | Indinavir AUC and C<sub>min</sub>: ↔ (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<sub>min</sub>: ↔ | 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. |

### CALCIUM CHANNEL BLOCKERS

<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HERBAL MEDICATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort (Hypericum perforatum) 300 mg TID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 54 %  Indinavir C\textsubscript{min}: ↓ 81 % (Relative to Indinavir 800 mg TID alone) Reduction in indinavir concentrations due to induction of drug metabolising and/or transport proteins by St. John’s wort.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>HISTAMINE H\textsubscript{2} ANTAGONIST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine 600 mg BID (Indinavir 400 mg SD)</td>
<td>Indinavir AUC and C\textsubscript{min}: ↔ (Relative to Indinavir 400 mg SD alone)</td>
<td>Indinavir and cimetidine can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>HMG-CoA REDUCTASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin, simvastatin</td>
<td>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.</td>
<td>Combination contraindicated due to an increased risk of myopathy including rhabdomyolysis.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Interaction not studied. Interaction study with Lopinavir/ritonavir + rosvastatin: Rosuvastatin AUC ↑ 2.08-fold Rosuvastatin C\textsubscript{max} ↑ 4.66-fold (Mechanism unknown)</td>
<td>Combination not recommended</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑ atorvastatin concentration Atorvastatin is less dependent on CYP3A4 for metabolism than lovastatin or simvastatin</td>
<td>Use the lowest possible dose of atorvastatin with careful monitoring. Caution is advised.</td>
</tr>
<tr>
<td>Pravastatin, fluvastatin</td>
<td>Interaction not studied Metabolism of pravastatin and fluvastatin is not dependent on CYP3A4. Interaction via effects on transport proteins cannot be excluded.</td>
<td>Interaction unknown. If no alternative treatment is available, use with careful monitoring.</td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Cyclosporine A (CsA) levels markedly increase in patients on PIs, including indinavir.</td>
<td>CsA levels require progressive dose adjustment using therapeutic drug monitoring.</td>
</tr>
<tr>
<td><strong>ORAL CONTRACEPTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethindrone/ethinyl estradiol 1/35 1 mcg QD (Indinavir 800 mg TID)</td>
<td>Norethindrone AUC: ↑ 26 % Norethindrone C\textsubscript{min}: ↑ 44 %</td>
<td>Indinavir and norethindrone/ethinyl estradiol 1/35 can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>----------------------------------------</td>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>PDE5 INHIBITOR</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Sildenafil 25 mg SD                     | 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. |
| (Indinavir 800 mg TID)                  |             |                                             |
| Vardenafil 10 mg SD                    | Vardenafil AUC: ↑ 16-fold  
Coadministration of CRIXIVAN with tadalafil 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. |
| (Indinavir 800 mg TID)                  |             |                                             |
| 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. Dosage 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 – INDINAVIR BOOSTED WITH RITONAVIR. 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”).
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD (Indinavir/ritonavir 800/100 BID)</td>
<td>Indinavir AUC: ↓ 25 % Indinavir C\textsubscript{min} ↓ 50 % (Relative to Indinavir/ritonavir 800/100 BID alone) Ritonavir AUC ↓ 36 % Ritonavir C\textsubscript{min} ↓ 39 % Efavirenz AUC and C\textsubscript{min} : ↔</td>
<td>Dose increases of indinavir/ritonavir when given in combination with efavirenz have not been studied.</td>
</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Interaction with indinavir/ritonavir not studied Decreased indinavir concentrations and increased rifabutin concentrations are expected.</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>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.</td>
<td>The combination of rifampicin and CRIXIVAN with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td><strong>Other Anti-infectives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Interaction with indinavir/ritonavir not studied Ritonavir induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when atovaquone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Erythromycin, Itraconazole</td>
<td>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.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole are concomitantly administered with indinavir/ritonavir.</td>
</tr>
</tbody>
</table>
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Product</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

### ANALGESICS

<table>
<thead>
<tr>
<th>Product</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Methadone</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Interaction with indinavir/ritonavir not studied Morphine levels may be decreased due to induction of glucuronidation by conadministered ritonavir.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when morphine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
</tbody>
</table>

### ANTIARRHYTMICS

<table>
<thead>
<tr>
<th>Product</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin 0.4 mg SD Ritonavir 200 mg BID</td>
<td>Interaction with indinavir/ritonavir not studied Digoxin AUC: ↑ 22 %</td>
<td>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.</td>
</tr>
</tbody>
</table>

### ANTICOAGULANT

<table>
<thead>
<tr>
<th>Product</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Ritonavir 400 mg BID</td>
<td>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.</td>
<td>Anticoagulation parameters should be monitored when warfarin is coadministered with indinavir/ritonavir.</td>
</tr>
</tbody>
</table>

### ANTICONVULSANTS

<table>
<thead>
<tr>
<th>Product</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of carbamazepine.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
</tbody>
</table>
Medicinal products by therapeutic areas | Interaction | Recommendations concerning co-administration
--- | --- | ---
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 dosage 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**

Dilitazem 120 mg QD (Indinavir/ritonavir 800/100 BID) | Dilitazem AUC<sub>0-24hr</sub>: † 43 % Indinavir/ritonavir AUCs: ↔ | Dose modification of calcium channel blockers should be considered when coadministered with indinavir/ritonavir as it may result in an increased response.

Amlodipine 5 mg QD (Indinavir/ritonavir 800/100 BID) | Amlodipine AUC<sub>0-24hr</sub>: † 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.

**PDE5 INHIBITOR**

Sildenafil, tadalafil | Interaction not studied. | For sildenafil and tadalafil, same recommendations as for indinavir without ritonavir boosting (see Table 1).
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vardenafil</td>
<td>Interaction not studied.</td>
<td>Vardenafil dose should not exceed a maximum of 2.5 mg in a 72-hour period when given with a boosted protease inhibitor.</td>
</tr>
</tbody>
</table>

#### SEDATIVES/HYPNOTICS

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>Interaction with indinavir/ritonavir not studied</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of buspirone.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Midazolam (parenteral)</td>
<td>Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally (CYP3A4 inhibition).</td>
<td>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. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.</td>
</tr>
</tbody>
</table>

#### STEROIDS

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>Interaction with indinavir/ritonavir not studied</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| Dexamethasone     | ↑ 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 section 4.2 and 5.2).

### 4.6 Pregnancy and lactation

#### Use during 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.

**Use during lactation**

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.

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, < 1/10); **Uncommon** (≥ 1/1,000, < 1/100); **Rare** (≥ 1/10,000, < 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.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>increases in MCV, decreases in neutrophils</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>increased spontaneous bleeding in patients with haemophilia, anemia including acute haemolytic anaemia, thrombocytopenia (see section 4.4).</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known*</td>
<td>anaphylactoid reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known*</td>
<td>new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, body fat changes (lipomatosis, lipoatrophy) (see section 4.4).</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>insomnia, hypoesthesia; paraesthesia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>oral paraesthesia.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>nausea, vomiting, diarrhoea, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>flatulence, dry mouth, acid regurgitation</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>hepatitis, including reports of hepatic failure, pancreatitis.</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very Common</td>
<td>isolated asymptomatic hyperbilirubinaemia, increased ALT and AST</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>liver function abnormalities</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>rash, dry skin</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>pruritus</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>rash including erythema multiforme and Stevens Johnson syndrome, hypersensitivity vasculitis, alopecia, hyperpigmentation, urticaria; ingrown toenails and/or paronychia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>myalgia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>myositis, rhabdomyolysis, increased CPK, osteonecrosis(see section 4.4).</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>haematuria, proteinuria, crystalluria</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>nephrolithiasis, dysuria.</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>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).</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>asthenia/fatigue, taste perversion, abdominal pain.</td>
</tr>
</tbody>
</table>

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (see section 4.4).

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 mc mol/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 dosage 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 Patients
In clinical trials in paediatric patients (≥ 3 years), the adverse experience 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 at the recommended dose. Asymptomatic pyuria of unknown etiology was noted in 10.9% (6/55) of pediatric patients who received CRIXIVAN at the recommended dose of 500 mg/m² every 8 hours. Some of these events were associated with mild elevation of serum creatinine.
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: 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 polypeptides that occurs during maturation of the newly formed viral particle. The resulting immature particles are non–infectious and are incapable of establishing new cycles of infection. Indinavir did not significantly inhibit the eukaryotic proteases human renin, human cathepsin D, human elastase, and human factor Xa.

Microbiology
Indinavir at concentrations of 50 to 100 nM mediated 95 % inhibition (IC95) of viral spread (relative to an untreated virus–infected control) in human T–lymphoid cell cultures and primary human monocytes/macrophages infected with HIV–1 variants LAI, MN, RF, and a macrophage–tropic variant SF–162, respectively. Indinavir at concentrations of 25 to 100 nM mediated 95 % inhibition of viral spread in cultures of mitogen–activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV–1, including isolates resistant to zidovudine and non–nucleoside reverse transcriptase inhibitors (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.

Drug 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/mm³.

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 naïve 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 patients
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/mm³; 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/mm³; 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 dosage 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 dosage regimen of 800 mg every 8 hours, HIV–seropositive adult patients in one study achieved geometric means of: AUC$_{0-8h}$ 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 dosage 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 0–12 hr, C_{max}, and C_{min} 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 dosage regimen of indinavir hard capsules, 500 mg/m² every 8 hours, produced AUC$_{0-12hr}$ 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. Crizivan, 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 drug 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 drug–induced renal injury. An increase in thyroidal weight and thyroidal follicular cell hyperplasia, due to an increase in thyroxine clearance, was seen in rats treated with indinavir at doses \( \geq 160 \text{ mg/kg/day} \). An increase in hepatic weight occurred in rats treated with indinavir at doses \( \geq 40 \text{ mg/kg/day} \) and was accompanied by hepatocellular hypertrophy at doses \( \geq 320 \text{ mg/kg/day} \).

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)
- silicon dioxide
- sodium lauryl sulphate
- 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

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 180 capsules.

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

7. MARKETING AUTHORISATION HOLDER
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)
EU/1/96/024/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
Date of first authorisation: 04/10/1996
Date of latest renewal: 07/10/2006

10. DATE OF REVISION OF THE TEXT
Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
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: Each 200 mg capsule contains 74.8 mg lactose.

For a 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, adolescents, and children 4 years of age and older. In adolescents and children, the benefit of indinavir therapy versus the increased risk of nephrolithiasis should particularly be considered (see section 4.4).

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).

**Adults**

The recommended dosage of CRIXIVAN 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).

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

**Children and adolescents (4 to 17 years of age)**

The recommended dosage of CRIXIVAN for patients 4 to 17 years of age is 500 mg/m² (dose adjusted from calculated body surface area [BSA] based on height and weight) orally every 8 hours (see table below). This dose should not exceed the equivalent of the adult dose of 800 mg every 8 hours. CRIXIVAN hard capsules should only be given to children who are able to swallow hard capsules. CRIXIVAN has not been studied in children under the age of 4 years (see section 5.1 and 5.2).
Paediatric dose (500 mg/m²) to be administered every 8 hours

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>CRIXIVAN dose Every 8 hours (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>300</td>
</tr>
<tr>
<td>0.75</td>
<td>400</td>
</tr>
<tr>
<td>1.00</td>
<td>500</td>
</tr>
<tr>
<td>1.25</td>
<td>600</td>
</tr>
<tr>
<td>1.50</td>
<td>800</td>
</tr>
</tbody>
</table>

General administration recommendations
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.

To ensure adequate hydration, it is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours. It is also recommended that children who weigh less than 20 kg drink at least 75 ml/kg/day and that children who weigh 20 to 40 kg drink at least 50 ml/kg/day.

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 (see section 4.4).

Special dosing considerations in adults

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

In patients with mild–to–moderate hepatic impairment due to cirrhosis, the dosage of CRIXIVAN 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).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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, 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 should not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecainide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Ritonavir should not be given with indinavir 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 and paediatric patients. The frequency of nephrolithiasis is higher in paediatric patients than in adult patients. 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. Paediatric patients who experience flank pain should be evaluated for the possibility of nephrolithiasis. Evaluation may consist of urinalysis, serum BUN and creatinine, and ultrasound of the bladder and kidneys. The long–term effects of nephrolithiasis in paediatric patients are unknown. Adequate hydration is recommended in all patients on indinavir (see section 4.2 and 4.8).

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 such as children, 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 effects.

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 rosvastatin 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).
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.

Hyperglycaemia
New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors (PIs). In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Fat redistribution
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

The safety and efficacy of indinavir/ritonavir has not been established in patients with significant underlying liver disorders and should not be used in this patient population.

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.

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 dosage 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 drug 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). This quantity is not likely to induce symptoms of lactose intolerance (milk intolerance).

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

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

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, 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.

Drugs 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 – UNBOOSTED INDINAVIR

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”).

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
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<th>Recommendations concerning co-administration</th>
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<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
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<tr>
<td><strong>Antiretrovirals</strong></td>
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<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td>Didanosine Formulation with buffer</td>
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<td></td>
</tr>
<tr>
<td>Didanosine enteric-coated 400 mg SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Indinavir 800 mg SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir: ↔</td>
<td></td>
<td>Can be administered without any restrictions</td>
</tr>
<tr>
<td>(Relative to Indinavir 800 mg SD alone)</td>
<td></td>
<td>with respect to time of administration or food.</td>
</tr>
<tr>
<td>Didanosine: ↔</td>
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<tr>
<td>Stavudine 40 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Indinavir 800 mg TID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir AUC: ↔</td>
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<td></td>
</tr>
<tr>
<td>Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Relative to Indinavir 800 mg TID alone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine AUC: ↑ 21 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine C&lt;sub&gt;min&lt;/sub&gt;: not evaluated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine 200 mg TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Indinavir 1,000 mg TID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir AUC: ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Relative to Indinavir 1,000 mg TID alone)</td>
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<td></td>
</tr>
<tr>
<td>Zidovudine AUC: ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine C&lt;sub&gt;min&lt;/sub&gt;: ↑ 51 %</td>
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<td></td>
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<tr>
<td>Lamivudine AUC: ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td></td>
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<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
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<tr>
<td><strong>NNRTIs</strong></td>
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</tbody>
</table>
| Delavirdine 400 mg TID (Indinavir 600 mg TID) | Indinavir AUC: ↑ 53 %  
Indinavir C<sub>min</sub>: ↑ 298 %  
(Relative to Indinavir 800 mg TID alone) | Dose reduction of CRIXIVAN to 400-600 mg every 8 hours should be considered. |
| Delavirdine 400 mg TID Indinavir 400 mg TID | Indinavir AUC: ↔  
Indinavir C<sub>min</sub>: ↑ 118 %  
(Relative to Indinavir 800 mg TID alone)  
Delavirdine: ↔ |                                               |
| Efavirenz 600 mg QD (Indinavir 1,000 mg TID) | Indinavir AUC: ↓ 46 %  
Indinavir C<sub>min</sub>: ↓ 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. | No specific dose recommendation can be given. |
| Efavirenz 200 mg QD (Indinavir 800 mg TID) | Indinavir AUC: ↓ 31 %  
Indinavir C<sub>min</sub>: ↓ 40 %  
Efavirenz AUC: ↔ |                                               |
| 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. |
<p>| 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). |</p>
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| **Ritonavir 100 mg BID** (Indinavir 800 mg BID) | Indinavir AUC_{24hr}: ↑178 %  
Indinavir C_{min}: ↑111-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}: ↑1266 %  
Indinavir C_{min}: ↑124-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}: ↑1220 %  
Indinavir C_{min}: ↑24-fold;  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC: ↔  
Ritonavir AUC_{24hr}: ↔ | |
| **Ritonavir 400 mg BID** (Indinavir 400 mg BID) | Indinavir AUC_{24hr}: ↑168 %  
Indinavir C_{min}: ↑10-fold;  
(Relative to Indinavir 800 mg TID alone*)  
Ritonavir AUC: ↔  
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

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| **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 |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
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<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
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<tr>
<td>Sulphamethoxazole/Trimethoprim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg/160 mg BID (Indinavir 400 mg QID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: † † (Relative to Indinavir 400 mg QID alone) Sulphamethoxazole AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and sulphamethoxazole/trimethoprim can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole 400 mg QD (Indinavir 1,000 mg TID)</td>
<td>Indinavir AUC: ↓ 24 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 1,000 mg TID alone)</td>
<td>Indinavir and fluconazole can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Itraconazole 200 mg BID (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: †† Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 49 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended with administering itraconazole concurrently.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: ↓ 20 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 29 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 400 mg TID)</td>
<td>Indinavir AUC: ↓ 56 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 27 % (Relative to Indinavir 800 mg TID alone)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
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<tr>
<td>Isoniazid 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 800 mg TID alone) Isoniazid AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and isoniazid can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Rifabutin 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 34 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 39 % (Relative to Indinavir 800 mg TID alone)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifabutin 150 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 32 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 40 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC*: ↑ 54 % Rifabutin C&lt;sub&gt;min&lt;/sub&gt;: ↑ 99 % (Relative to rifabutin 300 mg QD alone. No data has been obtained comparing rifabutin 150 mg QD in combination with indinavir 800 mg QD with a reference dose of 150 mg rifabutin alone)</td>
<td></td>
</tr>
<tr>
<td>Rifampicin 600 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 92 % (Relative to Indinavir 800 mg TID alone) This effect is due to an induction of CYP3A4 by rifampicin.</td>
<td>The use of rifampicin with indinavir is contraindicated.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
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</tr>
<tr>
<td><strong>ANALGESICS</strong></td>
<td></td>
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</tr>
<tr>
<td>Methadone 20-60 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ (Relative to Indinavir 800 mg TID historical controls) Methadone AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and methadone can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine 200 mg SD (Indinavir 400 mg SD)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 400 mg SD) † Quinidine concentration expected (CYP3A4 inhibition by indinavir)</td>
<td>Caution is warranted and therapeutic concentration monitoring is recommended for quinidine when coadministered with CRIXIVAN. The use of indinavir/ritonavir with quinidine is contraindicated.</td>
</tr>
<tr>
<td><strong>ANTIASTHMATIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline 250 mg SD (Indinavir 800 mg TID)</td>
<td>Theophylline AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and theophylline can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Not studied, combined administration may result in increased warfarin levels.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, phenobarbital phenytoin</td>
<td>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.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with indinavir.</td>
</tr>
<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine 50 mg TID (Indinavir 800 mg SD)</td>
<td>Indinavir AUC: † 28 % (Relative to Indinavir 800 mg SD alone) Venlafaxine and active metabolite O-desmethyl-venlafaxine: ↔</td>
<td>The clinical significance of this finding is unknown.</td>
</tr>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
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<tr>
<td>Dihydropyridine: e.g., felodipine, nifedipine, nicardipine</td>
<td>† dihydropyridine calcium channel blocker concentration</td>
<td>Caution is warranted and clinical monitoring of patients is recommended.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
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<tr>
<td><strong>HERBAL MEDICATIONS</strong></td>
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</table>
| St. John’s wort (Hypericum perforatum) 300 mg TID (Indinavir 800 mg TID) | Indinavir AUC: ↓ 54 %  
Indinavir Cmin: ↓ 81 %  
(Relative to Indinavir 800 mg TID alone)  
Reduction in indinavir concentrations due to induction of drug 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 H₂ ANTAGONIST**             |             |                                               |
| Cimetidine 600 mg BID (Indinavir 400 mg SD) | Indinavir AUC and Cmin: ↔  
(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 drug monitoring. |
| **ORAL CONTRACEPTIVES**               |             |                                               |
| Norethindrone/ethinyl estradiol 1/35 1 mcg QD (Indinavir 800 mg TID) | Norethindrone AUC: ↑ 26 %  
Norethindrone Cmin: ↑ 44 % | Indinavir and norethindrone/ethinyl estradiol 1/35 can be co-administered without dose adjustment. |
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<th>Medicinal products by therapeutic areas</th>
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<tbody>
<tr>
<td><strong>PDE5 INHIBITOR</strong></td>
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</table>
| 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. Dosage 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 – INDINAVIR BOOSTED WITH RITONAVIR. 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

<table>
<thead>
<tr>
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<tbody>
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<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD</td>
<td>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} : ↔</td>
<td>Dose increases of indinavir/ritonavir when given in combination with efavirenz have not been studied.</td>
</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Interaction with indinavir/ritonavir not studied Decreased indinavir concentrations and increased rifabutin concentrations are expected.</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>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.</td>
<td>The combination of rifampicin and CRIXIVAN with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td><strong>Other Anti-infectives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Interaction with indinavir/ritonavir not studied Ritonavir induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when atovaquone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Erythromycin, Itraconazole</td>
<td>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.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole are concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>ANALGESICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Methadone</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Interaction with indinavir/ritonavir not studied Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when morphine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.4 mg SD Ritonavir 200 mg BID</td>
<td>Interaction with indinavir/ritonavir not studied Digoxin AUC: ↑ 22 %</td>
<td>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.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin Ritonavir 400 mg BID</td>
<td>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.</td>
<td>Anticoagulation parameters should be monitored when warfarin is coadministered with indinavir/ritonavir.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of carbamazepine.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Divalproex, lamotrigine, phenytoin</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

**ANTIDEPRESSANTS**

| Trazodone 50 mg SD | 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 dosage 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 AUC0-24hr: ↑ 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 AUC0-24hr: ↑ 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. |

**PDE5 INHIBITOR**

<p>| Sildenafil, tadalafil | Interaction not studied. | For sildenafil and tadalafil, same recommendations as for indinavir without ritonavir boosting (see Table 1). |</p>
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vardenafil</td>
<td>Interaction not studied.</td>
<td>Vardenafil dose should not exceed a maximum of 2.5 mg in a 72-hour period when given with a boosted protease inhibitor.</td>
</tr>
</tbody>
</table>

**SEDATIVES/HYPNOTICS**

<table>
<thead>
<tr>
<th>SEDATIVES/HYPNOTICS</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Interaction with indinavir/ritonavir not studied. Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of buspirone.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Midazolam (parenteral)</td>
<td>Interaction with indinavir/ritonavir Not studied, combined administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally (CYP3A4 inhibition).</td>
<td>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. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.</td>
</tr>
</tbody>
</table>

**STEROIDS**

<table>
<thead>
<tr>
<th>STEROIDS</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Interaction with indinavir/ritonavir not studied [↑ dexamethasone exposure expected (CYP3A inhibition). [↓ indinavir plasma concentrations may be expected (CYP3A induction).</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
</tbody>
</table>

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

**4.6 Pregnancy and lactation**

**Use during 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.

**Use during lactation**

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.

### 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, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥ 1/10,000, < 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.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>increases in MCV, decreases in neutrophils</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>increased spontaneous bleeding in patients with haemophilia, anemia including acute haemolytic anaemia, thrombocytopenia (see section 4.4).</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known*</td>
<td>anaphylactoid reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known*</td>
<td>new on set diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, body fat changes (lipomatosis, lipoatrophy) (see section 4.4).</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>insomnia, hypoesthesia; paraesthesia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>oral paraesthesia.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>nausea, vomiting, diarrhoea, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>flatulence, dry mouth, acid regurgitation</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>hepatitis, including reports of hepatic failure, pancreatitis.</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very</td>
<td>isolated asymptomatic hyperbilirubinaemia, increased ALT and AST</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>liver function abnormalities</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>rash, dry skin</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>pruritus</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>rash including erythema multiforme and Stevens Johnson syndrome, hypersensitivity vasculitis, alopecia, hyperpigmentation, urticaria; ingrown toenails and/or paronychia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>myalgia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>myositis, rhabdomyolysis, increased CPK, osteonecrosis(see section 4.4).</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>haematuria, proteinuria, crystalluria</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>nephrolithiasis, dysuria.</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>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).</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>asthenia/fatigue, taste perversion, abdominal pain.</td>
</tr>
</tbody>
</table>

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (see section 4.4).

**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 dosage 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 Patients**
In clinical trials in paediatric patients (≥ 3 years), the adverse experience 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 at the recommended dose. Asymptomatic pyuria of unknown etiology was noted in 10.9% (6/55) of pediatric patients who received CRIXIVAN at the recommended dose of 500 mg/m² every 8 hours. Some of these events were associated with mild elevation of serum creatinine.
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: 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 polypeptides that occurs during maturation of the newly formed viral particle. The resulting immature particles are non–infectious and are incapable of establishing new cycles of infection. Indinavir did not significantly inhibit the eukaryotic proteases human renin, human cathepsin D, human elastase, and human factor Xa.

Microbiology
Indinavir at concentrations of 50 to 100 nM mediated 95 % inhibition (IC95) of viral spread (relative to an untreated virus–infected control) in human T–lymphoid cell cultures and primary human monocytes/macrophages infected with HIV–1 variants LAI, MN, RF, and a macrophage–tropic variant SF–162, respectively. Indinavir at concentrations of 25 to 100 nM mediated 95 % inhibition of viral spread in cultures of mitogen–activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV–1, including isolates resistant to zidovudine and non–nucleoside reverse transcriptase inhibitors (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.

Drug 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/mm³.

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 naïve 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 patients
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/mm³; 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/mm³; 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 dosage regimen of 800 mg every 8 hours, measured peak plasma concentrations (Cmax) 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 dosage regimen of 800 mg every 8 hours, HIV-seropositive adult patients in one study achieved geometric means of: AUC0–8h 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 dosage 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: AUC0–12h 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 dosage regimen of indinavir hard capsules, 500 mg/m² every 8 hours, produced AUC0–8hr 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. Crizivan, 800 mg every 8 hours + zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day). The mean indinavir plasma \( \text{AUC}_{0-8\text{hr}} \) 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 \( (C_{\text{min}}) \) 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 \( \text{AUC} \) and an 86 % reduction in \( C_{\text{max}} \). Administration with light meals (e.g., dry toast with jam or fruit conserve, apple juice, and coffee with skimmed or fat–free milk and sugar or corn flakes, skimmed or fat–free milk and sugar) resulted in plasma concentrations comparable to the corresponding fasted values.

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: \( \text{AUC}_{0-8\text{hr}} \) 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 drug 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 \( \text{AUC} \) 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 drug–induced renal injury. An increase in thyroidal weight and thyroidal follicular cell hyperplasia, due to an increase in thyroxine clearance, was seen in rats treated with indinavir at doses ≥ 160 mg/kg/day. An increase in hepatic weight occurred in rats treated with indinavir at doses ≥ 40 mg/kg/day and was accompanied by hepatocellular hypertrophy at doses ≥ 320 mg/kg/day.

The maximum non–lethal oral dose of indinavir was at least 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)
- silicon dioxide
- sodium lauryl sulphate
- 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 bottles 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

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

7. MARKETING AUTHORISATION HOLDER

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

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: 04/10/1996
Date of latest renewal: 07/10/2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.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: Each 400 mg capsule contains 149.6 mg of lactose.

For a 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, adolescents, and children 4 years of age and older. In adolescents and children, the benefit of indinavir therapy versus the increased risk of nephrolithiasis should particularly be considered (see section 4.4).

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).

Adults
The recommended dosage of CRIXIVAN 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).

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

Children and adolescents (4 to 17 years of age)
The recommended dosage of CRIXIVAN for patients 4 to 17 years of age is 500 mg/m² (dose adjusted from calculated body surface area [BSA] based on height and weight) orally every 8 hours (see table below). This dose should not exceed the equivalent of the adult dose of 800 mg every 8 hours. CRIXIVAN hard capsules should only be given to children who are able to swallow hard capsules. CRIXIVAN has not been studied in children under the age of 4 years (see section 5.1 and 5.2).
Paediatric dose (500 mg/m²) to be administered every 8 hours

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>CRIXIVAN dose Every 8 hours (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>300</td>
</tr>
<tr>
<td>0.75</td>
<td>400</td>
</tr>
<tr>
<td>1.00</td>
<td>500</td>
</tr>
<tr>
<td>1.25</td>
<td>600</td>
</tr>
<tr>
<td>1.50</td>
<td>800</td>
</tr>
</tbody>
</table>

**General administration recommendations**

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.

To ensure adequate hydration, it is recommended that adults drink at least 1.5 litres of liquids during the course of 24 hours. It is also recommended that children who weigh less than 20 kg drink at least 75 ml/kg/day and that children who weigh 20 to 40 kg drink at least 50 ml/kg/day.

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 (see section 4.4).

**Special dosing considerations in adults**

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

In patients with mild–to–moderate hepatic impairment due to cirrhosis, the dosage of CRIXIVAN 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).

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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, 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 should not be administered with alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encainide, flecainide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam and flurazepam.

Ritonavir should not be given with indinavir 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 and paediatric patients. The frequency of nephrolithiasis is higher in paediatric patients than in adult patients. 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. Paediatric patients who experience flank pain should be evaluated for the possibility of nephrolithiasis. Evaluation may consist of urinalysis, serum BUN and creatinine, and ultrasound of the bladder and kidneys. The long–term effects of nephrolithiasis in paediatric patients are unknown. Adequate hydration is recommended in all patients on indinavir (see section 4.2 and 4.8).

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 such as children, 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 effects.

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).
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.

Hyperglycaemia
New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors (PIs). In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Fat redistribution
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

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 events. 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.

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 dosage 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 drug 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). This quantity is not likely to induce symptoms of lactose intolerance (milk intolerance).

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

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

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, 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, encaidine, flecanide, procainamide, 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.

Drugs 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 – UNBOOSTED INDINAVIR

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").

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation with buffer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach.</td>
<td>Can be administered without any restrictions with respect to time of administration or food.</td>
</tr>
<tr>
<td>Didanosine enteric-coated 400 mg SD (Indinavir 800 mg SD)</td>
<td>Indinavir: ↔ (Relative to Indinavir 800 mg SD alone) Didanosine: ↔</td>
<td>Indinavir and NRTIs can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Stavudine 40 mg BID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir Cmin: ↔ (Relative to Indinavir 800 mg TID alone) Stavudine AUC: ↑ 21 % Stavudine Cmin: not evaluated</td>
<td></td>
</tr>
<tr>
<td>Zidovudine 200 mg TID (Indinavir 1,000 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir Cmin: ↔ (Relative to Indinavir 1,000 mg TID alone) Zidovudine AUC: ↔ Zidovudine Cmin: ↑ 51 %</td>
<td></td>
</tr>
<tr>
<td>Zidovudine/Lamivudine 200/150 mg TID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir Cmin: ↔ (Relative to Indinavir 800 mg TID alone) Zidovudine AUC: ↑ 39 % Zidovudine Cmin: ↔ Lamivudine AUC: ↔ Lamivudine Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Delavirdine 400 mg TID (Indinavir 600 mg TID) | Indinavir AUC: ↑ 53 %  
Indinavir C_{min}: ↑ 298 %  
(Relative to Indinavir 800 mg TID alone) | Dose reduction of CRIXIVAN to 400-600 mg every 8 hours should be considered. |
| Delavirdine 400 mg TID Indinavir 400 mg TID | Indinavir AUC: ↔  
Indinavir C_{min}: ↑ 118 %  
(Relative to Indinavir 800 mg TID alone)  
Delavirdine: ↔ |                                               |
| Efavirenz 600 mg QD (Indinavir 1,000 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. | No specific dose recommendation can be given. |
| Efavirenz 200 mg QD (Indinavir 800 mg TID) | Indinavir AUC: ↓ 31 %  
Indinavir C_{min}: ↓ 40 %  
Efavirenz AUC: ↔ |                                               |
| 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. |
<p>| 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). |</p>
<table>
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<th>Medicinal products by therapeutic areas</th>
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<th>Recommendations concerning co-administration</th>
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<tbody>
<tr>
<td><strong>Ritonavir 100 mg BID</strong>&lt;br&gt;(Indinavir 800 mg BID)</td>
<td>Indinavir AUC:&lt;br&gt;$\uparrow$ 178 %&lt;br&gt;Indinavir C&lt;sub&gt;min&lt;/sub&gt;:&lt;br&gt;$\uparrow$ 111-fold;&lt;br&gt;(Relative to Indinavir 800 mg TID alone*)&lt;br&gt;Ritonavir AUC: $\uparrow$ 72 %&lt;br&gt;Ritonavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 62 %</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Ritonavir 200 mg BID</strong>&lt;br&gt;(Indinavir 800 mg BID)</td>
<td>Indinavir AUC:&lt;br&gt;$\uparrow$ 1266 %&lt;br&gt;Indinavir C&lt;sub&gt;min&lt;/sub&gt;:&lt;br&gt;$\uparrow$ 124-fold;&lt;br&gt;(Relative to Indinavir 800 mg TID alone*)&lt;br&gt;Ritonavir AUC: $\uparrow$ 96 %&lt;br&gt;Ritonavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 371 %</td>
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<tr>
<td><strong>Ritonavir 400 mg BID</strong>&lt;br&gt;(Indinavir 800 mg BID)</td>
<td>Indinavir AUC:&lt;br&gt;$\uparrow$ 1220 %&lt;br&gt;Indinavir C&lt;sub&gt;min&lt;/sub&gt;:&lt;br&gt;$\uparrow$ 24-fold;&lt;br&gt;(Relative to Indinavir 800 mg TID alone*)&lt;br&gt;Ritonavir AUC:&lt;br&gt;$\uparrow$ 72 %&lt;br&gt;Ritonavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 62 %</td>
<td></td>
</tr>
<tr>
<td><strong>Ritonavir 400 mg BID</strong>&lt;br&gt;(Indinavir 400 mg BID)</td>
<td>Indinavir AUC:&lt;br&gt;$\uparrow$ 168 %&lt;br&gt;Indinavir C&lt;sub&gt;min&lt;/sub&gt;:&lt;br&gt;$\uparrow$ 10-fold;&lt;br&gt;(Relative to Indinavir 800 mg TID alone*)&lt;br&gt;Ritonavir AUC:&lt;br&gt;$\uparrow$ 72 %&lt;br&gt;Ritonavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 62 %</td>
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<tr>
<td><strong>Ritonavir 100 mg BID</strong>&lt;br&gt;(Indinavir 400 mg BID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: $\leftrightarrow$&lt;br&gt;(Relative to Indinavir 800 mg TID alone*)</td>
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<tr>
<td>*historical controls</td>
<td></td>
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<tr>
<td><strong>Saquinavir 600 mg SD (hard gel capsule formulation)</strong>&lt;br&gt;(Indinavir 800 mg TID)</td>
<td>Saquinavir AUC: $\uparrow$ 500 %&lt;br&gt;Saquinavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 190 %&lt;br&gt;(Relative to saquinavir 600 mg SD (hard gel formulation) alone)</td>
<td>The appropriate doses for this combination, with respect to efficacy and safety, have not been established.</td>
</tr>
<tr>
<td><strong>Saquinavir 800 mg SD (soft gel capsule formulation)</strong>&lt;br&gt;(Indinavir 800 mg TID)</td>
<td>Saquinavir AUC: $\uparrow$ 620 %&lt;br&gt;Saquinavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 450 %&lt;br&gt;(Relative to saquinavir 800 mg SD (soft gel formulation) alone)</td>
<td></td>
</tr>
<tr>
<td><strong>Saquinavir 1,200 mg SD (soft gel capsule formulation)</strong>&lt;br&gt;(Indinavir 800 mg TID)</td>
<td>Saquinavir AUC: $\uparrow$ 360 %&lt;br&gt;Saquinavir C&lt;sub&gt;min&lt;/sub&gt;: $\uparrow$ 450 %&lt;br&gt;(Relative to saquinavir 1,200 mg (soft gel formulation) alone)</td>
<td>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&lt;sub&gt;8h&lt;/sub&gt; during co-administration with saquinavir</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
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<td>Recommendations concerning co-administration</td>
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<tr>
<td><strong>Antibiotics</strong></td>
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<tr>
<td>Sulphamethoxazole/Trimethoprim 800 mg/160 mg BID (Indinavir 400 mg QID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 400 mg QID alone) Sulphamethoxazole AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and sulphamethoxazole/trimethoprim can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
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<tr>
<td>Fluconazole 400 mg QD (Indinavir 1,000 mg TID)</td>
<td>Indinavir AUC: ↓ 24 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 1,000 mg TID alone)</td>
<td>Indinavir and fluconazole can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Itraconazole 200 mg BID (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: ↔ Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 49 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended with administering itraconazole concurrently.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 600 mg TID)</td>
<td>Indinavir AUC: ↓ 20 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↑ 29 % (Relative to Indinavir 800 mg TID alone)</td>
<td>Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered.</td>
</tr>
<tr>
<td>Ketoconazole 400 mg QD (Indinavir 400 mg TID)</td>
<td>Indinavir AUC: ↓ 56 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 27 % (Relative to Indinavir 800 mg TID alone)</td>
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</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
<td></td>
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</tr>
<tr>
<td>Isoniazid 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 800 mg TID alone) Isoniazid AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and isoniazid can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Rifabutin 300 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 34 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 39 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC: ↑ 173 % Rifabutin C&lt;sub&gt;min&lt;/sub&gt;: ↑ 244 % (Relative to rifabutin 300 mg QD alone)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifabutin 150 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 32 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 40 % (Relative to Indinavir 800 mg TID alone) Rifabutin AUC*: ↑ 54 % Rifabutin C&lt;sub&gt;min&lt;/sub&gt;: ↑ 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)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin 600 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 92 % (Relative to Indinavir 800 mg TID alone) This effect is due to an induction of CYP3A4 by rifampicin.</td>
<td>The use of rifampicin with indinavir is contraindicated.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
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<td>Recommendations concerning co-administration</td>
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</tr>
<tr>
<td><strong>ANALGESICS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Methadone 20-60 mg QD (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↔ (Relative to Indinavir 800 mg TID historical controls) Methadone AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and methadone can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Quinidine 200 mg SD (Indinavir 400 mg SD)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 400 mg SD) † Quinidine concentration expected (CYP3A4 inhibition by indinavir)</td>
<td>Caution is warranted and therapeutic concentration monitoring is recommended for quinidine when coadministered with CRIXIVAN. The use of indinavir/ritonavir with quinidine is contraindicated.</td>
</tr>
<tr>
<td><strong>ANTIASTHMATIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline 250 mg SD (Indinavir 800 mg TID)</td>
<td>Theophylline AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔</td>
<td>Indinavir and theophylline can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANT</strong></td>
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<tr>
<td>Warfarin</td>
<td>Not studied, combined administration may result in increased warfarin levels.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
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</tr>
<tr>
<td>Carbamazepine, phenobarbital phenytoin</td>
<td>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.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with indinavir.</td>
</tr>
<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine 50 mg TID (Indinavir 800 mg SD)</td>
<td>Indinavir AUC: † 28 % (Relative to Indinavir 800 mg SD alone) Venlafaxine and active metabolite O-desmethyl-venlafaxine: ↔</td>
<td>The clinical significance of this finding is unknown.</td>
</tr>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
<td></td>
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<tr>
<td>Dihydropyridine: e.g., felodipine, nifedipine, nicardipine</td>
<td>† dihydropyridine calcium channel blocker concentration</td>
<td>Caution is warranted and clinical monitoring of patients is recommended.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
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<tr>
<td><strong>HERBAL MEDICATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort (Hypericum perforatum) 300 mg TID (Indinavir 800 mg TID)</td>
<td>Indinavir AUC: ↓ 54 % Indinavir C&lt;sub&gt;min&lt;/sub&gt;: ↓ 81 % (Relative to Indinavir 800 mg TID alone) Reduction in indinavir concentrations due to induction of drug metabolising and/or transport proteins by St. John’s wort.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>HISTAMINE H&lt;sub&gt;2&lt;/sub&gt; ANTAGONIST</strong></td>
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<tr>
<td>Cimetidine 600 mg BID (Indinavir 400 mg SD)</td>
<td>Indinavir AUC and C&lt;sub&gt;min&lt;/sub&gt;: ↔ (Relative to Indinavir 400 mg SD alone)</td>
<td>Indinavir and cimetidine can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td><strong>HMG-CoA REDUCTASE INHIBITORS</strong></td>
<td></td>
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<tr>
<td>Lovastatin, simvastatin</td>
<td>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.</td>
<td>Combination contraindicated due to an increased risk of myopathy including rhabdomyolysis.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Interaction not studied. Interaction study with Lopinavir/ritonavir + rosvastatin: Rosuvastatin AUC ↑ 2.08-fold Rosuvastatin Cmax ↑ 4.66-fold (Mechanism unknown)</td>
<td>Combination not recommended</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑ atorvastatin concentration Atorvastatin is less dependent on CYP3A4 for metabolism than lovastatin or simvastatin</td>
<td>Use the lowest possible dose of atorvastatin with careful monitoring. Caution is advised.</td>
</tr>
<tr>
<td>Pravastatin, fluvastatin</td>
<td>Interaction not studied Metabolism of pravastatin and fluvastatin is not dependent on CYP3A4. Interaction via effects on transport proteins cannot be excluded.</td>
<td>Interaction unknown. If no alternative treatment is available, use with careful monitoring.</td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Cyclosporine A (CsA) levels markedly increase in patients on PIs, including indinavir.</td>
<td>CsA levels require progressive dose adjustment using therapeutic drug monitoring.</td>
</tr>
<tr>
<td><strong>ORAL CONTRACEPTIVES</strong></td>
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<tr>
<td>Norethindrone/ethinyl estradiol 1/35 1 mcg QD (Indinavir 800 mg TID)</td>
<td>Norethindrone AUC: ↑ 26 % Norethindrone C&lt;sub&gt;min&lt;/sub&gt;: ↑ 44 %</td>
<td>Indinavir and norethindrone/ethinyl estradiol 1/35 can be co-administered without dose adjustment.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
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</tr>
<tr>
<td><strong>PDE5 INHIBITOR</strong></td>
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</tbody>
</table>
| 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. Dosage 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 – INDINAVIR BOOSTED WITH RITONAVIR. 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”).
<table>
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<tr>
<td><strong>Antiretrovirals</strong></td>
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<tr>
<td>Amprenavir</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD (Indinavir/ritonavir 800/100 BID)</td>
<td>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} : ↔</td>
<td>Dose increases of indinavir/ritonavir when given in combination with efavirenz have not been studied.</td>
</tr>
<tr>
<td><strong>Anti-Mycobacterial</strong></td>
<td></td>
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</tr>
<tr>
<td>Rifabutin</td>
<td>Interaction with indinavir/ritonavir not studied Decreased indinavir concentrations and increased rifabutin concentrations are expected.</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>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.</td>
<td>The combination of rifampicin and CRIXIVAN with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td><strong>Other Anti-infectives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Interaction with indinavir/ritonavir not studied Ritonavir induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when atovaquone is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Erythromycin, Itraconazole</td>
<td>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.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole are concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
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</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>ANALGESICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Methadone</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Interaction with indinavir/ritonavir not studied Morphine levels may be decreased due to induction of glucuronidation by conadministered ritonavir.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when morphine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td><strong>ANTIARRHYTHMICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.4 mg SD Ritonavir 200 mg BID</td>
<td>Interaction with indinavir/ritonavir not studied Digoxin AUC: ↑ 22 %</td>
<td>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.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin Ritonavir 400 mg BID</td>
<td>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.</td>
<td>Anticoagulation parameters should be monitored when warfarin is coadministered with indinavir/ritonavir.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Interaction with indinavir/ritonavir not studied Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of carbamazepine.</td>
<td>Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with indinavir/ritonavir.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
</tbody>
</table>
|----------------------------------------|-------------|-------------------------------------------------
| 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 dosage 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\textsubscript{0-24hr}: ↑ 43 % Indinavir/ritonavir AUCs: ↔ | Dose modification of calcium channel blockers should be considered when coadministered with indinavir/ritonavir as it may result in an increased response. |
| Amlodipine 5 mg QD (Indinavir/ritonavir 800/100 BID) | Amlodipine AUC\textsubscript{0-24hr}: ↑ 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. |

**PDE5 INHIBITOR**

<p>| Sildenafil, tadalafil | Interaction not studied. | For sildenafil and tadalafil, same recommendations as for indinavir without ritonavir boosting (see Table 1). |</p>
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vardenafil</td>
<td>Interaction not studied.</td>
<td>Vardenafil dose should not exceed a maximum of 2.5 mg in a 72-hour period when given with a boosted protease inhibitor.</td>
</tr>
</tbody>
</table>

**SEDATIVES/HYPNOTICS**

<table>
<thead>
<tr>
<th>Buspirone</th>
<th>Interaction with indinavir/ritonavir not studied. Indinavir and ritonavir inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of buspirone.</th>
<th>Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with indinavir/ritonavir.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (parenteral)</td>
<td>Interaction with indinavir/ritonavir not studied. Combination administrations are expected to significantly increase concentrations of midazolam, particularly when midazolam is given orally (CYP3A4 inhibition).</td>
<td>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. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.</td>
</tr>
</tbody>
</table>

**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 section 4.2 and 5.2).

### 4.6 Pregnancy and lactation

**Use during 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.

**Use during lactation**

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.

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).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Headache</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Rash</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Dry skin</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>≥ 1/10</td>
</tr>
</tbody>
</table>

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥ 1/10,000, < 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.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Very common</td>
<td>increases in MCV, decreases in neutrophils</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>increased spontaneous bleeding in patients with haemophilia, anemia including acute haemolytic anaemia, thrombocytopenia (see section 4.4).</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Not known*</td>
<td>anaphylactoid reactions</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Not known*</td>
<td>new onset diabetes mellitus or hyperglycaemia, or exacerbation of pre-existing diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, body fat changes (lipomatosis, lipoatrophy) (see section 4.4).</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Very common</td>
<td>headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>insomnia, hypoesthesia; paraesthesia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>oral paraesthesia.</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Very common</td>
<td>nausea, vomiting, diarrhoea, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>flatulence, dry mouth, acid regurgitation</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>hepatitis, including reports of hepatic failure, pancreatitis.</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<td>Very Common</td>
<td>isolated asymptomatic hyperbilirubinaemia, increased ALT and AST</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>liver function abnormalities</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Very common</td>
<td>rash, dry skin</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>pruritus</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>rash including erythema multiforme and Stevens Johnson syndrome, hypersensitivity vasculitis, alopecia, hyperpigmentation, urticaria; ingrown toenails and/or paronychia</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Common</td>
<td>myalgia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>myositis, rhabdomyolysis, increased CPK, osteonecrosis (see section 4.4).</td>
</tr>
</tbody>
</table>
Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (see section 4.4).

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 dosage 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 Patients
In clinical trials in paediatric patients (≥ 3 years), the adverse experience 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 at the recommended dose. Asymptomatic pyuria of unknown etiology was noted in 10.9 % (6/55) of pediatric patients who received CRIXIVAN at the recommended dose of 500 mg/m² every 8 hours. Some of these events were associated with mild elevation of serum creatinine.
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: 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 (IC95) of viral spread (relative to an untreated virus–infected control) in human T–lymphoid cell cultures and primary human monocytes/macrophages infected with HIV–1 variants LAI, MN, RF, and a macrophage–tropic variant SF–162, respectively. Indinavir at concentrations of 25 to 100 nM mediated 95 % inhibition of viral spread in cultures of mitogen–activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV–1, including isolates resistant to zidovudine and non–nucleoside reverse transcriptase inhibitors (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.

Drug 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/mm³.

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 naïve 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 patients
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/mm³; 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/mm³; 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 dosage 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 dosage regimen of 800 mg every 8 hours, HIV–seropositive adult patients in one study achieved geometric means of: AUC_{0–8h} 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 dosage 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, C_{max}, and C_{min} 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 dosage regimen of indinavir hard capsules, 500 mg/m² 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
A 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_{\text{max}}. Administration with light meals (e.g., dry toast with jam or fruit conserve, apple juice, and coffee with skimmed or fat–free milk and sugar or corn flakes, skimmed or fat–free milk and sugar) resulted in plasma concentrations comparable to the corresponding fasted values.

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).

**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 drug 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 drug–induced renal injury. An increase in thyroidal weight and thyroidal follicular cell hyperplasia, due to an increase in thyroxine clearance, was seen in rats treated with indinavir at doses ≥ 160 mg/kg/day. An increase in hepatic weight occurred in rats treated with indinavir at doses ≥ 40 mg/kg/day and was accompanied by hepatocellular hypertrophy at doses ≥ 320 mg/kg/day.

The maximum non–lethal oral dose of indinavir was at least 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)
- silicon dioxide
- sodium lauryl sulphate
- printing ink: titanium dioxide (E 171), indigo carmine (E 132) and iron oxide (E 172).

6.2 Incompatibilities

Not applicable.
6.3 Shelf life

2 years for HDPE bottles containing 18 hard capsules.
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 18, 90 or 180 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/004
EU/1/96/024/005
EU/1/96/024/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04/10/1996
Date of latest renewal: 07/10/2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORIZATION
A. MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

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

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 6.0 (of 22 June 2009) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

The Marketing Authorisation Holder will continue to submit annual Periodic Safety Update Reports.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### 1. NAME OF THE MEDICINAL PRODUCT

CRIXIVAN 100 mg hard capsules
Indinavir

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains indinavir sulphate corresponding to 100 mg of indinavir.

### 3. LIST OF EXCIPIENTS

Anhydrous lactose. See leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules

### 5. METHOD AND ROUTES OF ADMINISTRATION

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

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

Keep out of the reach and sight 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 Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRIXIVAN 100 mg
### PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

**CRIXIVAN 100 mg – pack of 180 capsules – Bottle label**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRIXIVAN 100 mg hard capsules</td>
</tr>
<tr>
<td>Indinavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains indinavir sulphate corresponding to 100 mg of indinavir.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous lactose. See leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTES OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Hard capsules should be swallowed whole.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desiccant should not be removed from the container.</td>
</tr>
<tr>
<td>Desiccant should not be swallowed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture.</td>
</tr>
</tbody>
</table>
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 Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/024/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
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

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

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

Keep out of the reach and sight 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 Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORIZAION 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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRIXIVAN 200 mg
<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRIXIVAN 200 mg hard capsules</td>
</tr>
<tr>
<td>Indinavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains indinavir sulphate corresponding to 200 mg of indinavir.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous lactose. See leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 hard capsules</td>
</tr>
<tr>
<td>270 hard capsules</td>
</tr>
<tr>
<td>360 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTES OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Hard capsules should be swallowed whole.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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</thead>
<tbody>
<tr>
<td>Desiccant should not be removed from the container.</td>
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<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
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 Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CRIXIVAN 400 mg – packs of 90, 180 and 18 capsules – Outer carton**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRIXIVAN 400 mg hard capsules</td>
</tr>
<tr>
<td>Indinavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous lactose. See leaflet for further information.</td>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 hard capsules</td>
</tr>
<tr>
<td>180 hard capsules</td>
</tr>
<tr>
<td>18 hard capsules</td>
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</tbody>
</table>

<table>
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<th>5. METHOD AND ROUTES OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
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<th>8. EXPIRY DATE</th>
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</thead>
<tbody>
<tr>
<td>EXP</td>
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</tbody>
</table>
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 Limited  
Hertford Road, Hoddesdon  
Hertfordshire EN11 9BU  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/96/024/004</td>
<td>90 hard capsules</td>
</tr>
<tr>
<td>EU/1/96/024/005</td>
<td>180 hard capsules</td>
</tr>
<tr>
<td>EU/1/96/024/008</td>
<td>18 hard capsules</td>
</tr>
</tbody>
</table>

13. **BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

CRIXIVAN 400 mg
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
CRIXIVAN 400 mg – packs of 90, 180 and 18 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
18 hard capsules

5. METHOD AND ROUTES OF ADMINISTRATION

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

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

Keep out of the reach and sight 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 Limited  
Hertford Road, Hoddesdon  
Hertfordshire EN11 9BU  
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

- EU/1/96/024/004 90 hard capsules  
- EU/1/96/024/005 180 hard capsules  
- EU/1/96/024/008 18 hard capsules

### 13. BATCH NUMBER

Batch

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What CRIXIVAN is and what it is used for
2. Before you take CRIXIVAN
3. How to take CRIXIVAN
4. Possible side effects
5. How to store CRIXIVAN
6. Further information

1. WHAT CRIXIVAN IS AND WHAT IT IS USED FOR

Pharmacotherapeutic Group
CRIXIVAN is a member of a class of medicinal products called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the number of HIV particles in blood.

Therapeutic Indications
CRIXIVAN should be used in combination with other antiretroviral agents for the treatment of HIV–1 infected adult and paediatric patients.

CRIXIVAN has been shown to help reduce the risk of developing illnesses associated with HIV disease. CRIXIVAN has also been shown to help lower the amount of HIV in your body (called “viral load”) and raise your CD4 (T) cell count. CD4 cells play a role in maintaining a healthy immune system to help fight infection. CRIXIVAN may not have these effects in all patients.

2. BEFORE YOU TAKE CRIXIVAN

Do not take CRIXIVAN
- if you are allergic (hypersensitive) to indinavir or any of the other ingredients of CRIXIVAN. Signs and symptoms of an allergic reaction may include: itchy skin, redness of the skin, wheals or hives, swelling of the face, lips, tongue and/or throat, or difficulty breathing.

Do not take CRIXIVAN with or without ritonavir
- if you take products containing rifampicin, amiodarone, terfenadine, astemizole, cisapride, alprazolam, triazolam, oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety), pimozide ergot derivatives such as ergot tartramine and ergot tartramine with caffeine, St. John's wort (Hypericum perforatum), simvastatin or lovastatin.

In addition, do not take CRIXIVAN with ritonavir
- if you take products containing alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encaïnide, lecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, stazolam, and flurazepam.
- if you have decompensated liver disease.
When CRIXIVAN is used with ritonavir, please tell your doctor and refer to the package leaflet for ritonavir for more information.

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

HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

**Bone problems**
Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Tell your doctor
- about any past or present medical problems, including liver disease due to cirrhosis;
- if you have kidney problems (including back pain with or without blood in your urine);
- if you have allergies;
- if you have high cholesterol and if you are taking cholesterol–lowering medicines called “statins”;
- if you have diabetes;
- if you have haemophilia;
- if you are intolerant to lactose because each hard capsule contains 37.4 mg lactose (anhydrous).

**Children**
CRIXIVAN can be taken by children 4 years of age and older who are able to swallow hard capsules.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There are some medicines that should not be taken with CRIXIVAN with or without ritonavir (see Do not take CRIXIVAN) or that require dosage changes of that medicine or CRIXIVAN (e.g., itraconazole, ketoconazole, cyclosporine, nevirapine, delavirdine and efavirenz).
Consult your doctor before taking certain cholesterol–lowering medicines (e.g., atorvastatin, rosuvastatin, pravastatin, fluvastatin), antifungals (e.g., fluconazole), anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine), steroids (e.g., dexamethasone), protease inhibitors (e.g., amprenavir, saquinavir, atazanavir), medicines for impotence (e.g., sildenafil), blood thinners (e.g., warfarin), calcium channel blockers (e.g., amlodipine, felodipine–class of medicinal products used for the treatment of hypertension and some specific heart disorders), sedative agents (e.g. midazolam administered by injection), antidepressants (e.g., venlafaxine), oral contraceptives (e.g. "the Pill"), medicines for asthma (e.g., theophylline) or any other medicines.

CRIXIVAN may be taken with a number of medicines that are commonly used in HIV infection (zidovudine, didanosine, lamivudine, stavudine, quinidine, cimetidine, clarithromycin, isoniazid, fluconazole, trimethoprim/sulfamethoxazole, methadone).

Some medications may interact with CRIXIVAN taken in combination with ritonavir. Please consult with your physician regarding taking medications with CRIXIVAN and ritonavir.

**Taking CRIXIVAN with food and drink**
CRIXIVAN should be taken without food but with water. If co-administered with ritonavir, CRIXIVAN may be administered with or without food. If water is not preferred, CRIXIVAN can be taken with skimmed or low–fat milk, juice, coffee, or tea.
If CRIXIVAN cannot be taken without food, a low–fat light meal, such as dry toast with jam or fruit conserve, juice and coffee with skimmed or low–fat milk and sugar, or a light meal such as corn flakes with skimmed or low–fat milk and sugar is acceptable.

Taking CRIXIVAN with a meal that is high in calories, fat, and protein reduces your body’s ability to absorb the medicine and in turn reduces its effectiveness.

**Pregnancy and breast-feeding**
Tell your doctor if you are pregnant or intend to become pregnant.
If you are pregnant, you should take CRIXIVAN only if your doctor decides it is clearly needed. It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman.
Tell your doctor if you are 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.

**Driving and using machines**
There is no specific information to suggest that CRIXIVAN affects your ability to drive and use machinery. However, dizziness and blurred vision have been reported during treatment with CRIXIVAN. Do not drive or operate machines if you experience these symptoms.

**Important information about some of the ingredients of CRIXIVAN**
This medicinal product contains 299.2 mg of lactose in each 800-mg dose (maximum single dose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE CRIXIVAN

Always take Crixivan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose for adults is 800 mg every 8 hours. An alternative dosing schedule for adults is CRIXIVAN 400 mg with ritonavir 100 mg both administered orally twice a day.

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

For all dosages, use a combination of the 100 mg, 200 mg or 400 mg hard capsules, as appropriate.
CRIXIVAN must be taken at regular intervals of 8 hours for full effectiveness and either 1 hour before or 2 hours after a meal.

CRIXIVAN should be swallowed unchewed together with water.

It is important for adults to drink at least 1.5 litres (approximately 48 fluid ounces) of liquids during each day while taking CRIXIVAN to help reduce the risk of forming kidney stones. It is also important for children and adolescents to drink enough liquids during the course of the day. The doctor will tell you the amount of liquids your child should drink.

Your doctor will tell you how long the treatment with CRIXIVAN will last.

**If you take more CRIXIVAN than you should**
In clinical studies, doses higher than 800 mg every 8 hours have not been shown to have any better effect.

Contact your doctor if you have taken more than the prescribed dose of CRIXIVAN.
The most common signs and symptoms of overdose are: nausea, vomiting, diarrhoea, back pain and blood in the urine. There is at present little information on the treatment of overdosage.

**If you forget to take CRIXIVAN**
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 prescribes. Do not stop taking it because reducing or missing doses will increase the risk of the HI–Virus becoming resistant to CRIXIVAN, in which case treatment with this medicine will become ineffective.

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

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, CRIXIVAN can cause side effects, although not everybody gets them. The following terms are used to describe how often side effects have been reported.

**Very common** (occurring in at least 1 in 10 patients treated)
**Common** (occurring in at least 1 of 100 and less than 1 of 10 patients treated)
**Not known** (cannot be estimated from the available data)

**Blood and the lymphatic disorders:**
Not known: low red blood cell count

**Immune system disorders:**
Not known: allergic reactions (sometimes severe, including shock)

**Nervous system disorders:**
Very common: dizziness; headache;
Common: inability to sleep decreased or abnormal skin sensation
Not known: numbness of the mouth

**Gastrointestinal disorders:**
Very common: nausea; vomiting; diarrhoea; an uncomfortable feeling in the stomach or belching after eating
Common: wind; dry mouth; acid regurgitation
Not known: inflammation of the pancreas; inflammation of the liver; liver failure
Skin and subcutaneous tissue disorders:
Very common: dry skin; rash
Common: itching
Not known: severe skin reactions; hair loss; darkening skin colour; ingrown toenails with or without infection

Musculoskeletal connective tissue and bone disorders:
Common: muscle pain

Renal and urinary disorders:
Common: pain on urination
Not known: infection of the kidneys, decreased kidney function, loss of renal function.

General disorders and administration site conditions:
Very common: weakness/fatigue; taste perversion; abdominal pain/swelling.

Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

There have been reports of inflammation of the kidneys and kidney stones. In some of these patients, this led to more severe kidney problems including kidney failure. In most cases, kidney impairment and kidney failure were reversible. Call your doctor if you develop sudden severe back pain, with or without blood in the urine, caused by kidney stones.

Your doctor will want to test your blood regularly to detect possible abnormalities such as rapid breakdown of red blood cells (anaemia), elevation of liver enzyme levels, impairment of kidney function, changes in blood sugar levels (hyperglycaemia).

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

Inform your doctor as soon as possible if you develop severe muscle pain or weakness. Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with cholesterol–lowering medicines called “statins”. There have also been reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues in patients not taking statins. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CRIXIVAN

Keep out of the reach and sight of children.

Do not use CRIXIVAN after the expiry date stated on the bottle or carton. The expiry date refers to the last day of the month.
Store CRIXIVAN in the original bottle. Keep the bottle tightly closed in order to protect from moisture. The bottles contain desiccant canisters that should remain in the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CRIXIVAN contains

- The active substance is indinavir sulphate. Each hard capsule contains indinavir sulphate corresponding to 100 mg of indinavir.
- The other excipients are anhydrous lactose, magnesium stearate, gelatin, silicon dioxide, sodium lauryl sulphate 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 look like and content of the pack

CRIXIVAN 100 mg hard capsules are supplied in HDPE bottles with a polypropylene cap and a foil induction cap containing 180 capsules.

The capsules are semi-translucent white and coded CRIXIVAN™ 100 mg in green.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer: Merck Sharp & Dohme B.V., Waarderweg 39, Postbus 581, 2003 PC Haarlem, The Netherlands

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

Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.ema.europa.eu
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What CRIXIVAN is and what it is used for
2. Before you take CRIXIVAN
3. How to take CRIXIVAN
4. Possible side effects
5. How to store CRIXIVAN
6. Further information

1. WHAT CRIXIVAN IS AND WHAT IT IS USED FOR

Pharmacotherapeutic Group
CRIXIVAN is a member of a class of medicinal products called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the number of HIV particles in blood.

Therapeutic Indications
CRIXIVAN should be used in combination with other antiretroviral agents for the treatment of HIV–1 infected adult and paediatric patients.

CRIXIVAN has been shown to help reduce the risk of developing illnesses associated with HIV disease. CRIXIVAN has also been shown to help lower the amount of HIV in your body (called “viral load”) and raise your CD4 (T) cell count. CD4 cells play a role in maintaining a healthy immune system to help fight infection. CRIXIVAN may not have these effects in all patients.

2. BEFORE YOU TAKE CRIXIVAN

Do not take CRIXIVAN
- if you are allergic (hypersensitive) to indinavir or any of the other ingredients of CRIXIVAN. Signs and symptoms of an allergic reaction may include: itchy skin, redness of the skin, wheals or hives, swelling of the face, lips, tongue and/or throat, or difficulty breathing.

Do not take CRIXIVAN with or without ritonavir
- if you take products containing rifampicin, amiodarone, terfenadine, astemizole, cisapride, alprazolam, triazolam, oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety), pimozide ergot derivatives such as ergot tartramine and ergot tartramine with caffeine, St. John's wort (Hypericum perforatum), simvastatin or lovastatin.

In addition, do not take CRIXIVAN with ritonavir
- if you take products containing alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encaidine, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam, and flurazepam.
- if you have decompensated liver disease.

When CRIXIVAN is used with ritonavir, please tell your doctor and refer to the package leaflet for ritonavir for more information.

**Take special care with CRIXIVAN**

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

HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

**Bone problems**

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Tell your doctor
- about any past or present medical problems, including liver disease due to cirrhosis;
- if you have kidney problems (including back pain with or without blood in your urine);
- if you have allergies;
- if you have high cholesterol and if you are taking cholesterol-lowering medicines called “statins”;
- if you have diabetes;
- if you have haemophilia;
- if you are intolerant to lactose because each hard capsule contains 74.8 mg lactose (anhydrous).

**Children**

CRIXIVAN can be taken by children 4 years of age and older who are able to swallow hard capsules.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There are some medicines that should not be taken with CRIXIVAN with or without ritonavir (see Do not take CRIXIVAN) or that require dosage changes of that medicine or CRIXIVAN (e.g., itraconazole, ketoconazole, cyclosporine, nevirapine, delavirdine and efavirenz).
Consult your doctor before taking certain cholesterol-lowering medicines (e.g., atorvastatin, rosuvastatin, pravastatin, fluvastatin), antifungals (e.g., fluconazole), anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine), steroids (e.g., dexamethasone), protease inhibitors (e.g., amrenavir, saquinavir, atazanavir), medicines for impotence (e.g., sildenafil), blood thinners (e.g., warfarin), calcium channel blockers (e.g., amlodipine, felodipine—class of medicinal products used for the treatment of hypertension and some specific heart disorders), sedative agents (e.g., midazolam administered by injection), antidepressants (e.g., venlafaxine), oral contraceptives (e.g., "the Pill"), medicines for asthma (e.g., theophylline) or any other medicines.

CRIXIVAN may be taken with a number of medicines that are commonly used in HIV infection (zidovudine, didanosine, lamivudine, stavudine, quinidine, cimetidine, clarithromycin, isoniazid, fluconazole, trimethoprim/sulfamethoxazole, methadone).

Some medications may interact with CRIXIVAN taken in combination with ritonavir. Please consult with your physician regarding taking medications with CRIXIVAN and ritonavir.

**Taking CRIXIVAN with food and drink**
CRIXIVAN should be taken without food but with water. If co-administered with ritonavir, CRIXIVAN may be administered with or without food. If water is not preferred, CRIXIVAN can be taken with skimmed or low-fat milk, juice, coffee, or tea. If CRIXIVAN cannot be taken without food, a low-fat light meal, such as dry toast with jam or fruit conserve, juice and coffee with skimmed or low-fat milk and sugar, or a light meal such as corn flakes with skimmed or low-fat milk and sugar is acceptable.

Taking CRIXIVAN with a meal that is high in calories, fat, and protein reduces your body’s ability to absorb the medicine and in turn reduces its effectiveness.

**Pregnancy and breast-feeding**
Tell your doctor if you are pregnant or intend to become pregnant. If you are pregnant, you should take CRIXIVAN only if your doctor decides it is clearly needed. It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman. Tell your doctor if you are 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.

**Driving and using machines**
There is no specific information to suggest that CRIXIVAN affects your ability to drive and use machinery. However, dizziness and blurred vision have been reported during treatment with CRIXIVAN. Do not drive or operate machines if you experience these symptoms.

**Important information about some of the ingredients of CRIXIVAN**
This medicinal product contains 299.2 mg of lactose in each 800-mg dose (maximum single dose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE CRIXIVAN

Always take Crixivan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose for adults is 800 mg every 8 hours. An alternative dosing schedule for adults is CRIXIVAN 400 mg with ritonavir 100 mg both administered orally twice a day.

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

For all dosages, use a combination of the 100–mg, 200–mg or 400–mg hard capsules, as appropriate.
CRIXIVAN must be taken at regular intervals of 8 hours for full effectiveness and either 1 hour before or 2 hours after a meal.

CRIXIVAN should be swallowed unchewed together with water.

It is important for adults to drink at least 1.5 litres (approximately 48 fluid ounces) of liquids during each day while taking CRIXIVAN to help reduce the risk of forming kidney stones. It is also important for children and adolescents to drink enough liquids during the course of the day. The doctor will tell you the amount of liquids your child should drink.

Your doctor will tell you how long the treatment with CRIXIVAN will last.

If you take more CRIXIVAN than you should
In clinical studies, doses higher than 800 mg every 8 hours have not been shown to have any better effect.

Contact your doctor if you have taken more than the prescribed dose of CRIXIVAN. The most common signs and symptoms of overdose are: nausea, vomiting, diarrhoea, back pain and blood in the urine. There is at present little information on the treatment of overdosage.

If you forget to take CRIXIVAN
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 prescribes. Do not stop taking it because reducing or missing doses will increase the risk of the HI–Virus becoming resistant to CRIXIVAN, in which case treatment with this medicine will become ineffective.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, CRIXIVAN can cause side effects, although not everybody gets them. The following terms are used to describe how often side effects have been reported.

Very common (occurring in at least 1 in 10 patients treated)
Common (occurring in at least 1 of 100 and less than 1 of 10 patients treated)
Not known (cannot be estimated from the available data)

Blood and the lymphatic disorders:
Not known: low red blood cell count

Immune system disorders:
Not known: allergic reactions (sometimes severe, including shock)

Nervous system disorders:
Very common: dizziness; headache;
Common: inability to sleep decreased or abnormal skin sensation
Not known: numbness of the mouth

Gastrointestinal disorders:
Very common: nausea; vomiting; diarrhoea; an uncomfortable feeling in the stomach or belching after eating
Common: wind; dry mouth; acid regurgitation
Not known: inflammation of the pancreas; inflammation of the liver; liver failure
Skin and subcutaneous tissue disorders:
Very common: dry skin; rash
Common: itching
Not known: severe skin reactions; hair loss; darkening skin colour; ingrown toenails with or without infection

Musculoskeletal connective tissue and bone disorders:
Common: muscle pain

Renal and urinary disorders:
Common: pain on urination
Not known: infection of the kidneys, decreased kidney function, loss of renal function.

General disorders and administration site conditions:
Very common: weakness/fatigue; taste perversion; abdominal pain/swelling.

Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

There have been reports of inflammation of the kidneys and kidney stones. In some of these patients, this led to more severe kidney problems including kidney failure. In most cases, kidney impairment and kidney failure were reversible. Call your doctor if you develop sudden severe back pain, with or without blood in the urine, caused by kidney stones.

Your doctor will want to test your blood regularly to detect possible abnormalities such as rapid breakdown of red blood cells (anaemia), elevation of liver enzyme levels, impairment of kidney function, changes in blood sugar levels (hyperglycaemia).

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

Inform your doctor as soon as possible if you develop severe muscle pain or weakness. Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with cholesterol–lowering medicines called “statins”. There have also been reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues in patients not taking statins. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CRIXIVAN

Keep out of the reach and sight of children.

Do not use CRIXIVAN after the expiry date stated on the bottle or carton. The expiry date refers to the last day of the month.
Store CRIXIVAN in the original bottle. Keep the bottle tightly closed in order to protect from moisture. The bottles contain desiccant canisters that should remain in the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CRIXIVAN contains

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

What CRIXIVAN look like and content of the pack

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

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

Marketing Authorisation Holder and Manufacturer

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

Manufacturer: Merck Sharp & Dohme B.V., Waarderweg 39, Postbus 581, 2003 PC Haarlem The Netherlands

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) website: http://www.emea.europa.eu
Read all of this leaflet carefully before you start taking this medicine.
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1. WHAT CRIXIVAN IS AND WHAT IT IS USED FOR

Pharmacotherapeutic Group
CRIXIVAN is a member of a class of medicinal products called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the number of HIV particles in blood.

Therapeutic Indications
CRIXIVAN should be used in combination with other antiretroviral agents for the treatment of HIV–1 infected adult and paediatric patients.

CRIXIVAN has been shown to help reduce the risk of developing illnesses associated with HIV disease. CRIXIVAN has also been shown to help lower the amount of HIV in your body (called “viral load”) and raise your CD4 (T) cell count. CD4 cells play a role in maintaining a healthy immune system to help fight infection. CRIXIVAN may not have these effects in all patients.

2. BEFORE YOU TAKE CRIXIVAN

Do not take CRIXIVAN
- if you are allergic (hypersensitive) to indinavir or any of the other ingredients of CRIXIVAN. Signs and symptoms of an allergic reaction may include: itchy skin, redness of the skin, wheals or hives, swelling of the face, lips, tongue and/or throat, or difficulty breathing.

Do not take CRIXIVAN with or without ritonavir
- if you take products containing rifampicin, amiodarone, terfenadine, astemizole, cisapride, alprazolam, triazolam, oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety), pimozide ergot derivatives such as ergot tartramine and ergot tartramine with caffeine, St. John's wort (Hypericum perforatum), simvastatin or lovastatin.

In addition, do not take CRIXIVAN with ritonavir
- if you take products containing alfuzosin, meperidine, piroxicam, propoxyphene, bepridil, encaïnide, flecanide, propafenone, quinidine, fusidic acid, clozapine, clorazepate, diazepam, estazolam, and flurazepam.
- if you have decompensated liver disease.

When CRIXIVAN is used with ritonavir, please tell your doctor and refer to the package leaflet for ritonavir for more information.

**Take special care with CRIXIVAN**

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

HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

**Bone problems**

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Tell your doctor
- about any past or present medical problems, including liver disease due to cirrhosis;
- if you have kidney problems (including back pain with or without blood in your urine);
- if you have allergies;
- if you have high cholesterol and if you are taking cholesterol-lowering medicines called “statins”;
- if you have diabetes;
- if you have haemophilia;
- if you are intolerant to lactose because each hard capsule contains 149.6 mg lactose (anhydrous).

**Children**

CRIXIVAN can be taken by children 4 years of age and older who are able to swallow hard capsules.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There are some medicines that should not be taken with CRIXIVAN with or without ritonavir (see Do not take CRIXIVAN) or that require dosage changes of that medicine or CRIXIVAN (e.g., itraconazole, ketoconazole, cyclosporine, nevirapine, delavirdine and efavirenz).
Consult your doctor before taking certain cholesterol–lowering medicines (e.g., atorvastatin, rosuvastatin, pravastatin, fluoxetine), antifungals (e.g., fluconazole), anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine), steroids (e.g., dexamethasone), protease inhibitors (e.g., amprenavir, saquinavir, atazanavir), medicines for impotence (e.g., sildenafil), blood thinners (e.g., warfarin), calcium channel blockers (e.g., amlodipine, felodipine–class of medicinal products used for the treatment of hypertension and some specific heart disorders), sedative agents (e.g., midazolam administered by injection), antidepressants (e.g., venlafaxine), oral contraceptives (e.g., "the Pill"), medicines for asthma (e.g., theophylline) or any other medicines.

CRIXIVAN may be taken with a number of medicines that are commonly used in HIV infection (zidovudine, didanosine, lamivudine, stavudine, quinidine, cimetidine, clarithromycin, isoniazid, fluconazole, trimethoprim/sulfamethoxazole, methadone).

Some medications may interact with CRIXIVAN taken in combination with ritonavir. Please consult with your physician regarding taking medications with CRIXIVAN and ritonavir.

**Taking CRIXIVAN with food and drink**
CRIXIVAN should be taken without food but with water. If co-administered with ritonavir, CRIXIVAN may be administered with or without food. If water is not preferred, CRIXIVAN can be taken with skimmed or low–fat milk, juice, coffee, or tea. If CRIXIVAN cannot be taken without food, a low–fat light meal, such as dry toast with jam or fruit conserve, juice and coffee with skimmed or low–fat milk and sugar, or a light meal such as corn flakes with skimmed or low–fat milk and sugar is acceptable.

Taking CRIXIVAN with a meal that is high in calories, fat, and protein reduces your body’s ability to absorb the medicine and in turn reduces its effectiveness.

**Pregnancy and breast-feeding**
Tell your doctor if you are pregnant or intend to become pregnant. If you are pregnant, you should take CRIXIVAN only if your doctor decides it is clearly needed. It is not known whether CRIXIVAN is harmful to an unborn baby when taken by a pregnant woman. Tell your doctor if you are 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.

**Driving and using machines**
There is no specific information to suggest that CRIXIVAN affects your ability to drive and use machinery. However, dizziness and blurred vision have been reported during treatment with CRIXIVAN. Do not drive or operate machines if you experience these symptoms.

**Important information about some of the ingredients of CRIXIVAN**
This medicinal product contains 299.2 mg of lactose in each 800-mg dose (maximum single dose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE CRIXIVAN

Always take Crixivan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose for adults is 800 mg every 8 hours. An alternative dosing schedule for adults is CRIXIVAN 400 mg with ritonavir 100 mg both administered orally twice a day.

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

For all dosages, use a combination of the 100–mg, 200–mg or 400–mg hard capsules, as appropriate.
CRIXIVAN must be taken at regular intervals of 8 hours for full effectiveness and either 1 hour before or 2 hours after a meal.

CRIXIVAN should be swallowed unchewed together with water.

It is important for adults to drink at least 1.5 litres (approximately 48 fluid ounces) of liquids during each day while taking CRIXIVAN to help reduce the risk of forming kidney stones. It is also important for children and adolescents to drink enough liquids during the course of the day. The doctor will tell you the amount of liquids your child should drink.

Your doctor will tell you how long the treatment with CRIXIVAN will last.

**If you take more CRIXIVAN than you should**

In clinical studies, doses higher than 800 mg every 8 hours have not been shown to have any better effect.

Contact your doctor if you have taken more than the prescribed dose of CRIXIVAN. The most common signs and symptoms of overdose are: nausea, vomiting, diarrhoea, back pain and blood in the urine. There is at present little information on the treatment of overdosage.

**If you forget to take CRIXIVAN**

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 prescribes. Do not stop taking it because reducing or missing doses will increase the risk of the HI–Virus becoming resistant to CRIXIVAN, in which case treatment with this medicine will become ineffective.

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

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, CRIXIVAN can cause side effects, although not everybody gets them. The following terms are used to describe how often side effects have been reported.

- Very common (occurring in at least 1 in 10 patients treated)
- Common (occurring in at least 1 of 100 and less than 1 of 10 patients treated)
- Not known (cannot be estimated from the available data)

**Blood and the lymphatic disorders:**

Not known: low red blood cell count

**Immune system disorders:**

Not known: allergic reactions (sometimes severe, including shock)

**Nervous system disorders:**

- Very common: dizziness; headache;
- Common: inability to sleep decreased or abnormal skin sensation
- Not known: numbness of the mouth

**Gastrointestinal disorders:**

- Very common: nausea; vomiting; diarrhoea; an uncomfortable feeling in the stomach or belching after eating
- Common: wind; dry mouth; acid regurgitation
- Not known: inflammation of the pancreas; inflammation of the liver; liver failure
Skin and subcutaneous tissue disorders:
Very common: dry skin; rash
Common: itching
Not known: severe skin reactions; hair loss; darkening skin colour; ingrown toenails with or without infection

Musculoskeletal connective tissue and bone disorders:
Common: muscle pain

Renal and urinary disorders:
Common: pain on urination
Not known: infection of the kidneys, decreased kidney function, loss of renal function.

General disorders and administration site conditions:
Very common: weakness/fatigue; taste perversion; abdominal pain/swelling.

Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

There have been reports of inflammation of the kidneys and kidney stones. In some of these patients, this led to more severe kidney problems including kidney failure. In most cases, kidney impairment and kidney failure were reversible. Call your doctor if you develop sudden severe back pain, with or without blood in the urine, caused by kidney stones.

Your doctor will want to test your blood regularly to detect possible abnormalities such as rapid breakdown of red blood cells (anaemia), elevation of liver enzyme levels, impairment of kidney function, changes in blood sugar levels (hyperglycaemia).

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

Inform your doctor as soon as possible if you develop severe muscle pain or weakness. Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with cholesterol–lowering medicines called “statins”. There have also been reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues in patients not taking statins. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CRIXIVAN

Keep out of the reach and sight of children.

Do not use CRIXIVAN after the expiry date stated on the bottle or carton. The expiry date refers to the last day of the month.
Store CRIXIVAN in the original bottle. Keep the bottle tightly closed in order to protect from moisture. The bottles contain desiccant canisters that should remain in the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CRIXIVAN contains

- The active substance is indinavir sulphate. Each hard capsule contains indinavir sulphate corresponding to 400 mg of indinavir.
- The other excipients are anhydrous lactose, magnesium stearate, gelatin, silicon dioxide, sodium lauryl sulphate 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 look like and content of the pack

CRIXIVAN 400 mg hard capsules are supplied in HDPE bottles with a polypropylene cap and a foil induction cap containing 18, 90 or 180 capsules. Not all pack sizes may be marketed.

The capsules are semi-translucent white and coded CRIXIVAN™ 400 mg in green.

Marketing Authorisation Holder and Manufacturer

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