

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Crixivan. This scientific discussion has been updated until 1 October 2004. For information on changes after this date, please refer to module 8B.

1. Chemical, pharmaceutical and biological aspects

The active substance of Crixivan, indinavir, is used as the sulphate salt ethanolate. One gram of anhydrous freebase corresponds to 1.25 grams of the sulphate salt ethanolate. This form is freely soluble in aqueous solutions, but the solubility decreases at higher pH. Indinavir is highly hygroscopic at relative humidities above 60 %. It has two pKa values, 6.2 and 3.8, and the partition coefficient octanol/water (log P) is 2.7 at pH 7.

The primary degradation pathway for indinavir sulphate for both solid state and solution is amide bond hydrolysis to form lactone and aminoindanol. The degradation is humidity and temperature dependent.

Indinavir is a chiral molecule with 5 stereogenic centres and is used as a single isomer. It is stereoselectively prepared from chiral starting materials. The enantiomeric purity is ascertained by a combination of controls during the synthesis. The only stereoisomer observed in the drug substance is the 4-(R)-epimer, which is controlled by the impurity method for drug substance.

The drug substance is very pure. The limit for any single impurity is not more than 0.1 % and the limit for the sum of all impurities is not more than 0.5 %. However, due to the high doses to be given in clinical use (> 2 g/day), the qualification threshold as defined in the ICH guideline on impurities, is 0.05 %. One of the impurities is thus not qualified since the levels were low in the batches used in the toxicological studies. The limit for this impurity is therefore tightened to not more than 0.05 %.

Composition

Crixivan is formulated as capsules containing 200 mg and 400 mg of the active substance. They contain a high percentage of the drug substance and two excipients, anhydrous lactose and magnesium stearate. The ingredients are granulated to improve flowability. A dry granulation method is used to avoid exposure to moisture, which has been shown to promote degradation to a lactone and aminoindanol.

All clinical trial formulations were manufactured with the same composition as the market product. The formulation intended for market has remained unchanged throughout the development programme.

Development pharmaceuticals

The development work is adequately described. Early clinical studies revealed a more reproducible absorption when indinavir was administered as the sulphate salt compared with the free base. The sulphate salt was chosen for the development of the product. In order to accelerate the dosage form development and to facilitate manufacture of the drug product, a weight multiple capsule formulation was chosen for the development.

Anhydrous lactose was selected as a filler and binding aid because of its low moisture content, non hygroscopicity and good compactibility. Magnesium stearate provides the lubrication required for machinability.

In view of indinavir sulphate's moisture and temperature sensitivity, poor flowability and relatively loose bulk density, a dry granulation formulation with acceptable compressibility and consistent fill volume during encapsulation was developed.

The manufacturing process is adequately described. It is carried out under GMP at controlled humidity of the air in the manufacturing areas associated with roller compaction/milling and encapsulating (less than 33 %). Studies showed that the quality of the finished product is not compromised by the scale-up in production. In order to protect the product against moisture and subsequent degradation, the market

container will be a HDPE (high density polyethylene) bottle fitted with polypropylene plastic cap. Silica gel canisters are included as desiccant.

The result of the process development is a stable product with low batch-to-batch variation with the finished product specification.

Stereoisomerism

The stereochemistry is well under control during the synthesis. Racemisation after the synthesis is extremely unlikely since it would require inversion of the configuration of all stereogenic centres. The formation of epimers cannot be excluded but should be detectable by the purity tests applied.

Control of starting materials

Indinavir sulphate is stereoselectively prepared from chiral starting material in six steps.

The enantiomeric purity of the active substance and other ingredients is ensured by the route of manufacture and quality control on intermediate products (starting materials and intermediate indinavir free base) rather than a test for specific rotation.

The impurity profile of indinavir sulphate has been extensively evaluated and remains consistent throughout the development and the scale-up. Potential impurities from synthesis, stereoisomeric impurities and degradants have been identified. The impurities are minimised or removed by control on the reaction parameters and in-process controls. High humidity which leads to formation of degradants is avoided.

The synthetic procedure is comprehensively described, including procedures used in the early stage of the development. The minor changes in the route of synthesis during development have not resulted in changes in the impurity profile or the consistently low impurity levels.

Control of other ingredients

Anhydrous lactose, magnesium stearate as well as the components of the capsule shells comply with the requirements of the European Pharmacopoeia. To demonstrate compliance with Commission Directive 1999/82/EC and the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/1230/98 rev.1), satisfactory European Pharmacopoeia Certificates of Suitability have been provided for the magnesium stearate and the gelatin.

Control of packaging materials

Studies showed that the product has good stability and is adequately protected from moisture in the proposed packaging configuration. Capsules are packaged in a container composed of HDPE (high density polyethylene) fitted with a polypropylene plastic cap and containing desiccant.

The blister is made of polyamide/aluminium/PVC with push through lidding of aluminium with a heat seal coating. The capacity of the package materials to protect from moisture has been demonstrated along with sufficient data on stability.

Control of the finished product

The specifications of the finished product cover the appearance of the capsules identity, assay of drug substance, dose uniformity, dissolution test, test on degradation product and moisture content. At release, an assay limit of 95-105 % and a limit for the lactone is set to not more than 0.3%. Batch analyses data for several pilot scale lots used in clinical, safety and stability studies are submitted and demonstrate a consistent quality of the product and compliance with the stated specifications. Since the aminoindanol is produced in equimolar amount to the lactone, only the data of the lactone levels are provided. No degradation other than the lactone and the aminoindanol were observed in any of the stressed capsules.

Stability

The stability of indinavir sulphate was assessed under a variety of storage conditions and containers. The submitted data show that in the presence of moisture and/or elevated temperatures, the drug substance undergoes conversion to an amorphous material or to a hydrate crystal form and to the formation of degradation products i.e. lactone and several unidentified impurities occur.

The stability results presently available demonstrate that the drug substance is stable under the stated storage conditions. No degradation or crystal form changes occurred.

The finished product shelf life limits for assay and lactone content are 93-105 % and not more 1.5 %, respectively. The stability studies of the finished product show that the drug product is stable when stored in the original container tightly closed and protected from humidity.

The initial shelf life at the time of the Marketing Authorisation was 12 months. Based on the availability of additional stability data the shelf life for all strengths was extended to 36 months when capsules are presented in bottles. The stability data provided demonstrated that the specifications are all met and that the shelf life of 36 months is acceptable. The shelf life for the 400 mg capsules stored in blisters is 24 months.

Submission of full time stability data on production batches of the finished product is part of the follow-up measures.

The applicant should also develop a specific analysis method for one of the degradation products in Crixivan capsules and reassess the shelf life specifications for degradants when the complete results of the stability studies will be available.

Additional strengths for Crixivan hard capsules have been later approved following its first approval. A new strength containing 333 mg indinavir has been formulated with the same ingredients as for the two already approved strengths, except the pink ink, and is the exact weight multiple of the existing ones. Since this new strength is bracketed within the existing ones, no bioequivalence study is required. The other strength, containing 100 mg indinavir, has been developed to be used in children. The active substance, the other ingredients and the method of preparation of the finished product were similar to the ones already approved.

2. Toxicopharmacological aspects

The nature and the rationale of the testing programme is in accordance with the guidelines for testing conventional products for single agent use.

The protein products of the *gag* and *pol* HIV genes are produced initially as precursor polypeptides, which must subsequently undergo post-translational cleavage to generate the respective structural proteins and enzymes. Indinavir is an orally active peptidomimetic HIV-1 protease inhibitor. Inactivation of the HIV protease by competitive inhibition results in the production of immature, non-infectious HIV particles, thus blocking completion of the viral replication cycle.

Pharmacodynamics

Effects related to the proposed indication

Eight *in vitro* studies regarding the antiviral activity, mechanism of action and resistance development were submitted. No *in vivo* studies have been conducted.

Indinavir is a selective inhibitor of HIV-1 protease with little inhibitory activity against mammalian proteases. The IC_{50} values were 0.41 nM for HIV-1 protease and > 40000 nM against several human proteases. Indinavir is considerably less active against HIV-2 than against HIV-1. Antiretroviral efficacy of indinavir *in vitro* was demonstrated in human T-lymphoid cell cultures, PBM (peripheral blood mononuclear) cells and primary monocytes/macrophages using the p24 assay. IC_{95} values of 50 nM to 100 nM were reported for both laboratory strains of HIV-1 and clinical isolates.

Indinavir is a reversible inhibitor. *In vitro* activity was reversible upon removal of the drug from cells and proteolytic activity appeared to resume more rapidly for indinavir than for other protease inhibitors.

Potential antiretroviral activity of metabolites was not directly investigated, but one study indicates that human plasma and urine metabolites contributed little to enzyme inhibition.

Resistance

Studies on the emergence of indinavir resistant HIV-1 variants in patients, some initially on suboptimal doses, showed a decreased antiviral effect by 24 weeks of therapy (see III.4).

Correlation of phenotypic and genotypic changes in clinical isolates from selected patients after 24 weeks of therapy was determined and amino acid changes were further analysed by site directed mutagenesis. By and large, resistance emergence was associated with multiple and variable coexpression of amino acid substitutions at 11 protease sites, at least. On the basis of the available data, amendments to the SPC on resistance mutations have been introduced to correspond to the need for this kind of information among practising physicians.

Decreasing susceptibility seemed to be related to increasing numbers of amino acid substitutions. A minimal loss of susceptibility seemed to require the coexpression of specific combinations of 3 substitutions and a greater degree of resistance ($IC_{95} > 400$ nM) at least 4 to 5 substitutions. A minimum of 4 substitutions was required for broad cross-resistance. All indinavir-resistant primary viral variants were cross-resistant to ritonavir whilst resistance to saquinavir was variable.

In vitro studies showed that zidovudine resistant clinical isolates were sensitive to indinavir as would be expected from the different mechanisms of action.

One brief report indicating synergistic activity *in vitro* of indinavir with zidovudine, didanosine and an investigational non-nucleoside reverse transcriptase inhibitor has been submitted. The potential for synergistic toxic interactions was not studied.

Pharmacokinetics

The disposition of indinavir exhibited both species and gender differences. In rats, absorption was rapid and pH dependent and a bioavailability of about 24 % in female rats and about 12 % in male rats was calculated. Absorption was prolonged following repeated administration of indinavir.

Greater than proportional increases in C_{max} and AUC were often observed in rats and dogs given repeated oral doses at 10 mg/kg/day and 40 mg/kg/day. No consistent dose proportionality trend could be seen at higher doses. In dogs, bioavailability approached 100 % while in monkeys a low bioavailability of 12 % was reported. No clear gender differences have been detected in dogs and monkeys.

Indinavir had a low protein binding ranging from 60 to 70 % in all species. Distribution, studied only in albino rats, was wide. Most tissues except the brain had high levels of radioactivity. Indinavir was taken up into brain tissue only to a limited extent with a mean plasma/brain ratio of 0.18. Uptake into lymphatic tissue, considered to be the main site for HIV replication was apparent and levels about half those of plasma were detected at 0.5 to 1 hour post dose.

Indinavir was extensively metabolised in all species by cytochromes P450 dependent systems, the primary site of metabolism being the liver, with the intestine contributing little to metabolism. The predominant pathways of indinavir metabolism were N-dealkylation and hydroxylation. Qualitatively similar metabolic profiles were seen across species.

The major route of excretion was biliary with 76 to 86 % of a dose excreted into faeces and less than 14% in urine.

Toxicology

In general pharmacology studies, some cardiovascular and respiratory effects were reported in anaesthetised dogs given intravenous doses of 10 mg/kg/day of indinavir. Other studies in dogs and mice given intravenous or oral doses of 10 mg/kg/day did not indicate any biologically significant effects on major organs. Systemic exposure was however well below the expected clinical exposure in

several of these studies. The studies regarding general pharmacology were not conducted in compliance with Good Laboratory Practice principles.

All pivotal toxicity studies were in compliance with Good Laboratory Practice principles.

The acute toxicity in mice and rats of per os and intraperitoneal administered indinavir is low. The incidental oral intake of a large quantity of indinavir by humans is not anticipated to produce serious adverse effects.

The repeated dose toxicity and toxicokinetics of orally administered indinavir were studied in rats and dogs for up to 53 weeks. Shorter duration oral studies were conducted in mice (14 weeks) and monkeys (5 weeks). In oral studies, the animals were administered indinavir at doses causing dose-limiting toxicity except for monkeys. Toxicity studies including a recovery period were not submitted.

Toxicity after intravenous administration (16 days) was studied in rats and dogs. No treatment-related toxicity was noted after intravenous administration.

Treatment related mortality due to gastrointestinal toxicity occurred in rats and mice. The toxicity was likely related to local irritant effects (gastrointestinal irritation due to the high dose). The clinical dose of 800 mg (16 mg/kg in a 50 kg person) administered t.i.d. is at least 40 times lower than doses causing gastrointestinal toxicity in rats and mice. Therefore it is not considered to be associated with a significant risk of gastrointestinal toxicity in patients.

In dogs very little treatment related toxicity other than emesis was seen. The absence of toxicity may reflect the low systemic exposure (AUC), 1-1.5 higher than clinical exposure, in this species. The toxicokinetic data indicate that sufficiently high systemic exposure could not be attained in dog studies.

A low toxicity in monkeys was observed in the 5 week toxicity programme. The systemic exposure in female monkeys was approximately 2-3 times higher than clinical exposure and in male monkeys, lower or comparable with clinical exposure.

Indinavir was associated with increased hepatic weight in rats, mice and monkeys. A modest induction of CYP3A1 was also demonstrated in both mice and rats. There might be a possibility of similar hepatic changes in humans although the metabolic load is lower in patients at clinical doses.

The indinavir induced hyperbilirubemia, observed in some toxicity studies and in a few AIDS patients, was studied in rats and in *in vitro* systems. It may be explained by the inhibition of hepatic uptake of bilirubine as well as inhibition of acylglucuronidation. Indinavir is a competitive inhibitor of uridine diphosphate glucuronyl transferases (UDPGT) in *in vitro* systems. However, indinavir did not inhibit the enzymes involved in glucuronidation of p-nitrophenol.

An increase in thyroid weight and thyroid hyperplasia was observed in all rat toxicity studies at doses over 160 mg/kg/day. This is likely due to an increase of thyroxin clearance. This probably represents a species-specific phenomenon and is not predictive of similar responses in humans.

Crystalluria (crystals contain the parent drug free-base form) was observed in numerous rats administered indinavir at relatively low doses. Crystalluria was not observed in monkeys treated with indinavir at doses of 10 - 40 mg/kg b.i.d. It was observed in one monkey at 160-mg/kg/day b.i.d. and in one female dog given a high dose of indinavir (80 mg/kg/day). The crystals were not associated with drug-induced renal injury. In rats administered very high doses of indinavir, renal tubular necrosis and vacuolation were observed.

Serum biochemical, haematological and urinal analytical changes were noted in rats and mice exposed to indinavir concentrations in the clinical range. These changes seem to be of minor toxicological significance.

Repeated dose toxicity studies in rats and dogs given indinavir sulphate at doses up to 160 mg/kg/day together with two degradates did not show any effects indicative of additive or synergistic toxicity.

During the evaluation of the low strength of Crixivan intended to be used in children, the available toxicological data in young animals were reviewed. Results from a 14-week study in juvenile dogs (aged 1 day at start of the study) and a study in infant monkeys to specifically investigate

hyperbilirubinemia showed that there was no cause for specific concerns regarding toxic effects of indinavir in relation to the age of the organism. However, since no significant margins of exposure between plasma levels coupled to toxic effects in animals and expected therapeutic levels were identified, the safety of indinavir in HIV-infected children had to be assessed from clinical data.

Reproduction toxicity

Indinavir was investigated in fertility studies in male and female rats, in a developmental study in rabbits, in a developmental toxicity study in rats with postweaning evaluation, and a fostering/cross-fostering study in rats. Indinavir did not cause maternal toxicity in the rabbit developmental toxicity study at doses up to 240 mg/kg/day (systemic exposure approximately 1.5 times the clinical exposure). There was no developmental toxicity in the foetuses other than an increased incidence of reduced 13th rib that was of questionable significance. In rats, maternal toxicity was characterised by body weight changes and decreased food consumption. Developmental toxicity in F1 generation, probably due to accumulation of indinavir in the milk (ratio milk/plasma 1.2 to 1.5) of lactating rats, was manifested as decreases in pup weights during and after lactation, and as an increase over controls in the incidence of supernumerary rib and cervical ribs at systemic exposure levels below or comparable with clinical exposure. There was no evidence of teratogenicity.

As pointed out in section 4.6 of the SPC, data from studies in beagle dogs indicated a slight increase in the incidence of resorptions, but with no effects on viability of the foetus.

Indinavir crossed the placenta with significant foetal exposure occurring in rats (foetal plasma AUC value estimated to approximately 20 % of maternal plasma AUC), but minimal exposure to the drug in rabbits (foetal plasma AUC value estimated to approximately 2 % of maternal plasma AUC).

To further study the effect of indinavir during gestation and the postnatal period, a developmental toxicity study in dogs is in progress.

Genotoxic and carcinogenic potential

Carcinogenicity studies in mice were negative. In rats, an increased incidence of thyroid adenomas was seen, probably related to an increase in release of TSH secondary to an increase in thyroxine clearance. The relevance of the findings to humans is likely limited. The full carcinogenic potential of indinavir cannot be assessed due to systemic exposure levels only 2 to 3 times higher than the expected clinical exposure despite use of maximum tolerated doses. Results from genotoxicity tests were negative.

Local tolerance

The potential dermal and ocular irritating properties are not expected to be a safety concern during the intended therapy.

Environmental risk

Data submitted to evaluate the potential risk of indinavir on the environment suggested that no exposure levels of concern to the environment are to be expected.

3. Clinical aspects

The assessment of data relies on the impact on biological markers and an exploratory analysis of clinical efficacy. As reflected in the "Points to consider in the assessment of new anti-HIV medicinal products" adopted by the CPMP in January 1996, the information on biological markers was not sufficient to base an approval solely on these markers. It was felt that the predictivity of therapeutic changes in CD4 cell counts and viral load in terms of clinical benefits was either incomplete or not sufficiently evaluated.

Clinical pharmacology

Pharmacodynamic studies

In vitro indinavir concentrations of 25 to 100 nM achieved 95% inhibition of viral spread in HIV-1 infected cells (CIC₉₅). Human pharmacokinetic data indicate that a dose of 400 mg q 6h or 600 mg q 6h maintained mean blood levels above 100 nM throughout the dosing interval.

At the recommended dose regimen (800 mg t.i.d.), C_{max} was about 11000 nM and geometric mean trough concentration about 211 nM, which is above the CIC₉₅.

Microbiology and resistance

As discussed in part III, *in vitro* synergistic antiviral effects were observed in infected lymphoid cells when indinavir was combined with reverse transcriptase inhibitors.

As indicated in the dose-finding studies, suboptimal doses of indinavir led to subsequent loss of activity even after patients were switched to higher doses. The proportion of patients that developed resistance at 24 weeks was 13 % and 39 % in two studies. A direct comparison between indinavir monotherapy and combination therapy of indinavir and zidovudine showed that the combination conferred some protection against indinavir resistance. Moreover, the combination therapy of indinavir and zidovudine also protected from zidovudine resistance. With the triple combination indinavir-zidovudine-didanosine, these effects were statistically significant, with a reduction 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).

As anticipated, no cross-resistance with nucleoside analogues occurred. Complete cross-resistance between indinavir and ritonavir was demonstrated.

Approximately two thirds of viral clinical isolates tested at the time of the initial submission that were resistant to indinavir exhibited resistance to saquinavir. One half of these variants exhibited high level resistance to saquinavir.

Pharmacokinetic studies

Pharmacokinetic parameters were calculated by conventional non-compartmental methods. Information on the pharmacokinetics of indinavir in humans has been obtained from a total of 25 studies. Data from 374 subjects was presented, of whom 179 were HIV patients. The vast majority of the subjects included were male (84 %). One study was performed in subjects with mild to moderate hepatic impairment.

Indinavir is rapidly absorbed in the fasted state (T_{max} of 0.8 hours) with an absolute bioavailability of approximately 60 % within the dose range of 400 mg to 800 mg. The bioavailability of a single 800 mg dose was approximately 65 %. Administration of a 400 mg dose with a high-fat breakfast reduced the relative bioavailability to approximately 20 % compared to fasting conditions, whereas bioavailability was unaffected when an 800 mg dose was administered with a light meal. Following single doses of 600 and 800 mg indinavir in HIV patients, mean values of AUC and C_{max} were 13131 nM.h and 6853 nM, 24733 nM.h and 10134 nM, respectively.

Plasma protein binding of indinavir is about 60%. The binding was concentration independent in the range 0.05 to 10 µg/ml (80-16000 nM), which covers the range of plasma levels *in vivo* following administration of doses up to 800 mg t.i.d.

There are no data with regard to distribution into the central nervous system in humans. Preclinical data show an extensive distribution into the lymphatic system, but only limited distribution across the blood brain barrier with a ratio of drug concentration in the brain to that in plasma of 0.18.

Following single rising oral doses of 100-1000 mg of indinavir, area under the plasma concentration time curve (AUC_{0-24h}) increased greater than dose proportionally. The non-linear increase in plasma levels was also seen at steady state. This is suggested to result from a saturation of the first pass metabolism of indinavir during the absorption phase when the concentration of indinavir is very high.

During the elimination phase indinavir is rapidly eliminated with a terminal half-life of approximately 2 hours independent of the dose. Consistent with the short half-life, the accumulation of indinavir at steady state is rather modest.

Approximately 10 % of the dose is excreted unchanged in urine and the rest is eliminated through metabolism. Seven metabolites were identified *in vitro* following incubation with human liver microsomes. *In vitro* studies with human liver microsomes employing selective inhibitors and different P450 enzymes indicate that CYP3A4 and related 3A isozymes are the only enzymes that play a major role in the oxidative metabolism of indinavir. The *in vitro* metabolic profile was qualitatively confirmed *in vivo*.

No major pharmacokinetic differences were identified in Caucasians versus Blacks, or in HIV patients versus healthy volunteers. Although data in women are limited, no major gender differences in the pharmacokinetic profile of indinavir were identified.

There was only limited data available on the pharmacokinetics of indinavir in children following administration of the capsule formulation. With the development of the low capsule strength, the pharmacokinetics of indinavir have been studied in a total of 95 children and adolescents aged 3-18 years old, of which 70 received the recommended dose (500 mg/m² (dose adjusted from calculated body surface area)). The vast majority (72 %) were ≤ 11 years old, but with only one child younger than 4 years. Overall, the data presented indicated that, in HIV-infected paediatric patients, the indinavir dose of 500 mg/m² every 8 hours produced generally similar AUC_{0-8hr} compared to that observed in adults receiving the recommended indinavir dose of 800 mg every 8 hours. The geometric mean trough concentrations in paediatric patients were approximately one half of the values in adults. This constitutes a concern as it can not be excluded that trough levels of indinavir would not be of importance for efficacy/resistance development. Considering the high frequency of nephrolithiasis already seen in paediatric patients at the recommended dose, a higher dose did not seem to be an option.

No study has been performed in patients with renal insufficiency. There are no pharmacokinetic data for subjects older than 60 years. During the post-authorisation phase, a multiple dose study has been performed in HIV seropositive female patients to assess the pharmacokinetics of indinavir in women compared to males. There were no clinically significant differences in the pharmacokinetics of indinavir in HIV seropositive women compared to HIV seropositive men.

Due to increased drug exposure, a dose reduction to 600 mg t.i.d. is suggested in patients with mild to moderate hepatic insufficiency.

Interactions

An extensive drug interaction program (14 studies) was planned for indinavir with 12 studies completed at the time of the initial submission. Drugs were selected on the basis of the potential for pharmacokinetic interactions because of involvement with CYP3A4 and/or because they are frequently prescribed to HIV-infected patients. These findings are stated in the relevant parts of the Summary of Product Characteristics.

Preliminary results from two interaction studies with rifabutin demonstrated the difficulty to predict the effects of dose adjustments. Due to an increase in the plasma concentrations of rifabutin and a decrease in the plasma concentrations of indinavir, a dosage reduction of rifabutin to half the standard dose and a dosage increase of indinavir to 1000-1200 mg every 8 hours is suggested when rifabutin is coadministered with indinavir. This dose regimen has not been confirmed in clinical studies and could result in a clinically significant increase in the plasma concentrations of rifabutin. Results from a confirmatory study will be submitted.

Results from an interaction study with rifampicin confirmed that indinavir should not be used concurrently with rifampicin because coadministration results in 90 % reduction in indinavir plasma concentrations. Considering this dramatic effect, indinavir should be used cautiously with other drugs that are potent inducers of CYP3A4 (phenobarbital, phenytoin, dexamethasone and carbamazepine). Coadministration may result in decreased plasma concentrations of indinavir and as a consequence an increased risk for suboptimal treatment and facilitation of development of resistance.

Although no interaction study with warfarin has been performed an interaction leading to increased levels of warfarin can presently not be ruled out.

Results from an interaction study with theophylline (a substrate for CYP1A2 and 3A4) suggest that there is no clinically significant effect of indinavir on the pharmacokinetics of theophylline, and review of adverse experiences indicated that the combination was generally well tolerated. This has been reflected in the SPC, section 4.5.

Results from interaction studies with ketoconazole, itraconazole, nevirapine and delavirdine have been addressed in relevant parts of the SPC. These results have led to considerations on dose adjustments as indicated in the SPC section 4.2.

Further interaction data have shown that the co-administration of methadone with indinavir does not impact on the pharmacokinetics of either of these two products.

New interaction data of indinavir with other medicinal products have become available and therefore have led to an update of the information of the relevant section of the SPC.

Co-administration of efavirenz 200 mg, which is a substrate of CYP 3A4 and indinavir 800 mg tid for 14 days was shown to result in decreased indinavir AUC and C_{max} by 31 % and 16 % respectively. An increase of indinavir dose when both substances are co-is therefore at present recommended.

The possibility of interaction between indinavir and HMG-CoA reductase inhibitors, either or not predominantly metabolised by CYP3A4 cannot be excluded considering that indinavir inhibits CYP3A4 and that HMG-CoA reductase inhibitors are substrates for CYP3A4. Not all HMG-CoA reductase inhibitors have however CYP3A4 as a major elimination pathway (e.g. pravastatin) but all are substrates of the transporter P-glycoprotein (PgP). Thus the increased levels of HMG-CoA levels might arise from the interaction. There are no clinical data available on the combination of indinavir with HMG-CoA reductase inhibitors, not predominantly metabolised by CYP3A4 are not available but caution should be exercised when co-administrated.

Twice daily coadministration to volunteers of indinavir (800 mg) and ritonavir (100, 200, or 400 mg) with food for two weeks resulted in increased indinavir AUC_{24h} of 178 %, 266 %, and 220 %, respectively, compared to historical indinavir AUC_{24h} values (indinavir 800 mg every 8 hours alone). In addition, twice daily coadministration of indinavir (400 mg) and ritonavir (400 mg) resulted in increased indinavir AUC_{24h} of 68 %. In the same study, twice daily coadministration of indinavir (800 mg) and ritonavir (100 or 200mg) resulted in increased ritonavir AUC_{24h} of 72 % and 96 % respectively, versus the same doses of ritonavir alone. By contrast, twice daily coadministration of indinavir (800 mg and 400 mg) and ritonavir (400 mg) had a negligible effect (7 % and 7 % decrease respectively) on ritonavir AUC_{24h}. Currently, there are no safety or efficacy data available on the use of this combination in patients. As the risk of nephrolithiasis is a dose related phenomenon that is more likely to occur at high indinavir exposures, it was agreed to add a warning on the increased risk of nephrolithiasis, when the two substances are co-administered.

Coadministration of indinavir with saquinavir (600-mg hard capsules or 800-mg soft capsules or 1200-mg soft capsules single dose) in healthy subjects resulted in a 500 %, 620 %, and 360 % increase in saquinavir plasma AUC_{24h}, respectively. Relevant safety and efficacy data are not available for this combination. 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 coadministration with saquinavir.

Because indinavir is a cytochrome P-450 3A4 inhibitor, co-administration with sildenafil is likely to result in an increase of sildenafil plasma concentrations by competitive inhibition of metabolism. The magnitude of this interaction has not been determined. However, based on data on the co-administration of sildenafil with saquinavir and ritonavir, which have shown 210 % and 1000 % increases in sildenafil AUC an interaction cannot be excluded.

A published pharmacokinetic study has investigated the effect of repeated dosing with St John's Wort (*Hypericum perforatum*)(300 mg three times daily with meals) on the pharmacokinetics of indinavir (Lancet 2000; 355: 547-8)

Mean extrapolated AUC_{0-8h} of indinavir was reduced from $30.8 \pm 8.4 \mu\text{g.h/ml}$ to $12.3 \pm 4.7 \mu\text{g.h/ml}$ after treatment with St John's Wort, i.e. by approximately 60%. The extrapolated concentration 8 hours after dose was reduced from $0.49 \pm 0.44 \mu\text{g/ml}$ to $0.048 \pm 0.026 \mu\text{g/ml}$ by St John's Wort, i.e. by about 90%. C_{max} of indinavir was reduced by approximately 30%. Hence, St John's Wort caused a marked reduction in indinavir plasma levels. The results indicate that St John's Wort is an inducer of CYP3A4, which is involved in the metabolism of indinavir. The co-administration is therefore contraindicated.

Despite the fact that no reports of interactions have been reported so far, increased pimozone levels carry the risk of QT prolongation and ventricular arrhythmias. It is reasonable to expect an interaction between pimozone and protease inhibitors. Therefore, concomitant administration of pimozone and protease inhibitors should be contraindicated.

Clinical experience

The initial assessment of clinical efficacy relies on phase II and III studies with biological endpoints primarily measured until 24 weeks of therapy in 277 patients on indinavir monotherapy with the proposed dose, and 247 patients on combination therapies. The extension phase (48 weeks) comprised a limited number of patients.

The inclusion criteria covered a diverse spectrum, with CD4 cell counts ranging from 0-500 cells/mm³ (median levels at enrollment, 140 to 250). In fact, 35 % of patients were moderately immunosuppressed with CD4 levels of 250-300/mm³. A majority were young Caucasian males, and females represented 15 % of the patients in the phase III programme.

Pharmacodynamic studies

A total of 417 patients were enrolled in 8 phase II studies with a primary treatment period of 24 weeks. These studies investigated the effect of indinavir in monotherapy or in combination with nucleoside analogues on biological endpoints, i.e. CD4 cell counts and serum HIV RNA.

Combined results of these studies showed that the chosen dose of 800 mg q 8h exerted an optimal antiviral activity. Moreover, higher doses increased the risk of adverse events such as nephrolithiasis and hyperbilirubinemia.

The effect on viral load was temporary in patients receiving suboptimal doses whereas the effect on CD4 cell counts was maintained during the 24 weeks.

In these trials high viral load ($>20,000$ copies/ml) was an inclusion criterion and three phase II studies (studies 019, 020 and 035) were carried out in order to compare the effects of indinavir with nucleoside analogues (zidovudine, didanosine, lamivudine) over a 24 week period.

Study 019 was a double-blind study comparing the effect of indinavir, indinavir and zidovudine, and zidovudine. This study showed that the effect of indinavir alone or in combination with zidovudine was significantly superior to zidovudine alone. For indinavir patients at 24 weeks, 45 % on monotherapy and 59 % on combination treatment had $>2 \log_{10}$ viral load decrease from baseline. There were no statistically significant differences between the indinavir groups but the proportion of patients with undetectable virus at week 24 was 50 % for the combination group and 9 % for the monotherapy group.

Results of the following three early trials indicated a dramatic impact on viral replication as reflected by the magnitude and the duration of decrease in HIV-1 serum levels. The impact on CD4 cells was clear and sustained for the 24-week assessment period:

Study 020 was an open study comparing the effect of indinavir, indinavir/zidovudine/didanosine and zidovudine/didanosine.

A 2- \log_{10} viral load decrease was seen at week 24 in 18 % of patients with indinavir monotherapy and in 21 % of patients with zidovudine/didanosine and 53 % in the triple therapy group. Forty seven per cent of the triple combination patients had undetectable virus levels at 24 weeks.

Only the triple combination therapy with indinavir and two nucleoside analogues showed statistically significant superiority over indinavir monotherapy and conferred protection to emergence of resistance both to indinavir and the nucleosides analogues.

Study 035 was a 52 week randomised study comparing the effect of the triple combination indinavir/zidovudine/lamivudine, zidovudine/lamivudine and indinavir monotherapy.

Preliminary results of this trial, which were part of the initial submission, indicated a dramatic impact on viral replication as reflected by the magnitude and duration of decrease in HIV-1 serum levels. This protocol recruited 97 nucleoside-experienced patients (median ZDV 30 months) with a median CD4 count of 144 and a median baseline viral load of 4.6-log₁₀ copies/ml. At week 24, the proportion of patients with viral load below 500 copies/ml was 90 % (95 % CI 73; 98) for IDV/ZDV/LAM, for IDV 43 % (25; 63) and for ZDV/LAM 0 % (0; 12). Corresponding figures utilising the ultra-direct assay and viral load < 50 copies/ml were 68, 32 and 0 %, respectively. In 14/22 patients in the triple drug group, still no detectable viral RNA was detected with this assay at week 40. There were no confirmed AIDS events.

Confirmatory trials

There were five large-scale phase III trials. Two of those trials have primary clinical endpoints, study 028 in zidovudine naive patients and study ACTG 320 in zidovudine-experienced patients. Studies 033, 037 and 039 focus predominantly on biological endpoints. High levels of viral load were no inclusion criterion in contrast to the early trials.

The efficacy data in the original submission relied on analysis of biological endpoints derived from studies 028 and 033. These studies were both double blind, randomised and involved antiretroviral naive patients.

The following section will focus on the results of the clinical endpoint trials. Results of the biological endpoint trials are summarised in the table “Overview of efficacy trials”.

ACTG 320 recruited 1156 ZDV experienced patients with CD4 counts < 200 cells/mm³ (38 % of whom with CD4 cells < 50 cells/mm³) who were followed for a median of 38 weeks (range 0-52 weeks). In these patients, indinavir (800 mg q 8h), zidovudine (200 mg t.i.d.) and lamivudine (150 mg b.i.d.) 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 % (Intention to treat).

Study 028 recruited 996 treatment-naive patients with CD4 cells between 50 and 250 per mm³ who were followed for a median of 56 weeks (range 0-97 weeks). In these patients, indinavir (800 mg q 8h) with and without zidovudine (200 mg t.i.d.) compared with zidovudine alone reduced the probability of ADID at 48 weeks from 15 % to approximately 6 % (Intention to treat).

After cut-off date for both ACTG 320 and Protocol 028, additional deaths were reported to the DSMB. All data on mortality have been included in a meta-analysis. Overall, comparing IDV in combination with nucleoside analogues and nucleoside analogues alone, the results indicate that IDV may increase overall survival (HR 0.6, two-tailed p = 0.08). The study results from trial ACTG 320 demonstrated a probability of death of 4.2 % (IDV-) and 1.6 % (IDV+) at 48 weeks, corresponding to a hazard ratio of 0.43, p = 0.048 (CD4 < 50 cells: 0.4, p = 0.06; CD4 > 50 cells: 0.5, p = 0.5). In study 028 there were no significant differences.

In study ACTG 320, superiority with indinavir (IDV) was consistently demonstrated as regards changes in CD4 count and viral load in patients with more (CD4 < 50) or less (CD4 50 to 200) advanced disease. The proportion of patients with viral load below the limit of quantification in the IDV containing arm was, based on data from a randomly selected population, about 60 % at week 24 (vs. 9 %). In study 028, the proportion of patients with viral load below the limit of quantification was about 40 to 50 % in the IDV/ZDV group at weeks 24 to 80. In summary, the antiviral effect tends to remain stable over prolonged periods of follow-up in indinavir treated patients. Similarly, effects on CD4 cell count tend to be more pronounced among patients treated with IDV in combination with nucleoside analogues compared with nucleoside analogues. In study ACTG 320, the mean change from baseline at week 40 was 121 (IDV+) and 39 (IDV-) CD4 cells per mm³. In study, 028 the corresponding figures at week 40 were 139 (IDV/ZDV) and 12 (ZDV) CD4 cells per mm³.

Clinical efficacy in children

Two ongoing clinical trials have been designed to characterise the safety, antiretroviral activity, and pharmacokinetics of indinavir (500 mg/m² every 8 hour) in combination with stavudine and lamivudine: study 068 (n = 25 aged 4 to 15 years) and study ACTG 395 (n = 16 aged 5 to 13 years). Results from these studies are displayed below:

	Study	< 400 copies/ml (95 % CI)		< 50 copies/ml (95 % CI)	
Noncompleter = Failure	068 (24 weeks)	61 %	41; 81 %	48 %	27; 68 %
	068 (60 weeks)	56 %	37; 76 %	36 %	17; 55 %
	ACTG395 (24 weeks)	56 %	41; 81 %	50 %	26; 75 %
Observed Cases	068 (24 weeks)	78 %	59; 97 %	61 %	39; 84 %
	068 (60 weeks)	82 %	64; 100 %	64 %	39; 89 %
	ACTG395 (24 weeks)	75 %	59; 97 %	67 %	40; 93 %

Long-term data up to 60 weeks confirmed the durability of the effect of indinavir in combination with stavudine and lamivudine.

Clinical efficacy during pregnancy Study PATCG 358 was designed to investigate the pharmacokinetics (PK) of indinavir [IDV] (co-administered with lamivudine [3TC] and zidovudine [ZDV]) in HIV-1 infected pregnant patients between 14 to 28 weeks gestation at enrollment, who were without prior complications or conditions (medical, obstetrical, etc.) and were protease inhibitor naïve. The first patient entered the trial in 1998 and the last 2002. Pregnant patients took IDV 800 mg orally every 8 hours until 12 weeks postpartum. Maternal pharmacokinetic evaluation occurred at Week 30 to 32 gestation (antepartum) and 6 weeks postpartum (postpartum). Altogether 16 women entered the trial, but 11 were fully assessable, i.e. had full PK profiles ante- and post- partum. The first patient entered the trial in 1998 and the last 2002. The study report is dated August 2003. Different laboratories were used for the determination of indinavir concentration but within an individual patient the same laboratory was used.

Cord concentrations of IDV were evaluated in samples from 8 mother / infant pairs.

Table: Indinavir maternal pharmacokinetic parameters at antepartum and postpartum with indinavir. Pharmacokinetic parameters in non-pregnant patient historical controls when indinavir 800 mg q8h was given with 3TC and ZDV.

Indinavir Parameter	Antepartum (Week 30 to 32) (n=11)	Postpartum (Week 6) (n=11)	Nonpregnant Historical Controls (n=10) [†]	GMR 95% CI Antepartum/ Postpartum	GMR 95% CI Antepartum/ Historical Controls [‡]	GMR 95% CI Postpartum/ Historical Controls [‡]
AUC _{0-8h} (nM·h)	9231 [§]	34869 [§]	26597 [§]	0.26 (0.14, 0.50)	0.35 (0.17, 0.70)	1.31 (0.80, 2.15)
C _{max} (nM)	4999 [§]	13966 [§]	11683 [§]	0.36 (0.17, 0.75)	0.43 (0.19, 0.96)	1.20 (0.73, 1.97)
C _{min} (nM)	332 [†]	138 [†]	186 [†]	na	na	na
Range	(LOQ to 448)	(LOQ to 2403)	(70 to 425)			

[†] C_{min} are median values with ranges. For antepartum, 6 of 11 mother's had IDV plasma concentrations below assay limit of reliable quantification (LOQ) and for postpartum 4 of 11 mother's had plasma concentrations below LOQ and therefore, geometric means and GMRs were not calculated.

[‡] Historical control data from Protocol 053.

[§] Geometric mean values.

GMR = Geometric mean ratio.

95% CI = 95% confidence interval around the geometric mean ratio.

For 6 of the 8 mother / infant pairs, the IDV cord concentrations were below the LOQ of the assay. One sample gave no detectable peak and the other sample gave a concentration of 65.0 nM.

Reduced exposure levels of indinavir during pregnancy seem, at least partly, to relate to enzyme induction. Available data are much too sparse, however, to support a recommendation as regards use of indinavir in combination with zidovudine for the treatment of HIV infection during pregnancy. Further studies are clearly indicated, but indinavir is hardly the best candidate for such studies today.

The SPC sections 4.6 and 5.2 have been revised to reflect these data.

Safety

A total of about 2000 patients from phase I/II and ongoing phase III studies laid the basis for the initial safety assessment. However, a clear pattern emerged where dose-related events such as nephrolithiasis (4 %) and unconjugated hyperbilirubinemia (10 %) without hepatotoxicity were the most prominent features. Safety in females was only addressed in 10 % of the individuals in the phase II studies and in 15 % of the individuals in phase III.

A total of 249 patients in phase II trials were exposed for a mean duration of 149 days with a majority treated for 151 to 180 days. A majority were Caucasian (84 %) and males (90 %) with a mean age of 37 years. Approximately 20 % of the patients in the different treatment groups had AIDS, and 50 % had received previous antiretroviral therapy with zidovudine. The long-term follow-up of about 100 patients (48 weeks) did not disclose any new or increased frequencies of events. Two-phase III trials have included about 1400 patients with the proposed indinavir dose in monotherapy and in combination with zidovudine. Data from pharmacological studies (330 patients treated for a mean duration 10-14 days) were included.

Considering information from all sources, 12 deaths were noted. One was possibly associated with indinavir (hepatic failure).

The overall incidence rate of nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria) observed in the studies was approximately 10 %. These events occurred in between 2 days and 19 months following initiation of mono- or combination therapy with indinavir. The recommendation to consider reducing the dosage in patients with one or more episodes of nephrolithiasis was deleted because of lack of supporting clinical data.

During the authorisation procedure, there have been reports of increased bleeding including spontaneous skin haematomas and hemarthroses in type A and B haemophilic patients treated with protease inhibitors. In some patients, additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment was discontinued. A causal relationship has been suggested although the mechanism of action has not been elucidated. As these reports involved zidovudine, zalcitabine and indinavir, a class-related side effect has been suggested. Appropriate information to inform both health professionals and patients has been introduced in the warning section of the Summaries of Product Characteristics and in the Package Leaflets for the three compounds.

Safety in children

In HIV-infected paediatric patients who received IDV 500 mg/m² every 8 hours in combination with NRTIs, IDV is generally well tolerated with the exception of a higher frequency of nephrolithiasis in children (approximately 30%). As chronic interstitial nephritis is a slowly progressive process, possible effects on global kidney function after several years of therapy are difficult to predict based on available safety data.

Post Marketing experience

Reports of haemolysis or haemolytic anaemia were notified. A specific mention has been added to the warning section 4.4 of the Summary of Product Characteristics regarding the occurrence of hemolytic anaemia in patients treated with indinavir.

Several notifications of hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes mellitus have been reported in patients treated by the protease inhibitors. Both the Pharmacovigilance

Working Party and the Committee for Proprietary Medicinal Products (CPMP) have evaluated this information. During its meeting in June 1997, the CPMP recommended that the relevant specialist physicians in charge of HIV infected patients and prescribing these medicinal products should be informed through the National Competent Authorities. To that end, a "Dear Doctor" letter was prepared by this Committee and a common wording for the warning section of the SPCs for all protease inhibitors was agreed on.

Additional adverse events were reported in the post marketing experience: hepatitis and rare reports of hepatic failure, hyperpigmentation, abdominal distension, crystalluria, alopecia, anaphylactoid reactions, urticaria, rash including erythema multiforme and Stevens Johnson Syndrome; interstitial nephritis, nephrolithiasis, in some cases with renal insufficiency or acute renal failure; and increased serum triglycerides.

New adverse events have been reflected in relevant parts of the product information.

With regard to the first annual re-assessment, the results of the reported studies corroborate the safety profile of Crixivan as previously delineated in the SPC, although cases of rash including erythema multiforme and Stevens Johnson Syndrome have been described. The reported incidence of serious adverse events considered to be related to therapy was about 2 % without obvious difference between regimens containing IDV or not.

As mentioned in the interaction section above, the results of further interaction studies have been addressed in the relevant parts of the SPC. As indicated in section 4.2 of the SPC this may lead to considerations on dose adjustments.

Continuous assessment of Crixivan long-term safety profile is performed throughout PSURs and the product information updated accordingly

Events of special interest

Lipodystrophy

Further to reports from the literature on the association of protease inhibitors with adverse events such as fat redistribution and other metabolic disorders, additional information was presented. These data confirmed that combination antiretroviral therapy, including regimens containing a protease inhibitor, was associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Protease inhibitors may also be associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. The data provided did not permit any conclusion about the causality. A class labelling wording was however included into the SPC of all the protease inhibitors products, and further investigation will be performed to better define this adverse event.

Muscle-related reactions

Increased CPK, muscle-related reactions (myalgia, myosis and rarely rhabdomyolysis) have been reported with protease inhibitors. Although it was difficult to determine causality of these reactions due to confounding factors and scanty information, it was nevertheless considered necessary to update the relevant information on muscle-related adverse reactions of the Summary of Product Characteristics and to reflect this effect in the Package Leaflet.

Liver impairment in HIV positive patients

Further to the discussions held by the *Ad-hoc Group of Experts on Anti-HIV medicinal products* in November 2001, the CPMP agreed that liver impairment was of increasing concern in HIV positive patients both in the form of adverse hepatic effects in patients with normal liver function prior to antiretroviral treatment (ART) and as regards patients with chronic liver disease treated with ART.

In January 2002 the CPMP requested the MAH for all authorised anti-retroviral medicinal products to conduct a retrospective review of clinical trials and post marketing data relating to the use of their product(s) in patients with hepatic impairment and/or HBV/HCV co-infection. Following review of the submitted responses and discussions held during the CPMP meeting and the Pharmacovigilance

Working Party meeting in October 2002, the CPMP adopted a list of questions (including general, product specific and SPC wording recommendations).

The review of the MAHs' responses has essentially confirmed that co-infected patients and patients with underlying liver disorders are at increased risk for adverse events, essentially confined to liver events. Overall, there is a disturbing lack of general and product specific knowledge (e.g. relevant pharmacokinetic data in patients with liver impairment), but there are ongoing activities.

For some of the products still undergoing drug development, the MAHs have confirmed that co-infected patients will not be excluded from participation in the studies. The CPMP stressed that whenever feasible a minimum number of co-infected patients should be included in forthcoming studies in order to provide a reasonable basis for a relevant safety (and efficacy) analysis.

Following the review of responses submitted by all MAHs of antiretroviral medicinal products, a class labelling on "liver disease" has been agreed and implemented in the product information for all antiretroviral medicinal products.

The SPC of Crixivan has been reworded in accordance with the CPMP recommendations to include, in section 5.2, data on AUC, C_{max} and C_{min} (including CV) derived from patients. These PK results in patients give a more reliable description of the concentrations achieved in clinical practice at the recommended dose.

4. Overall conclusions and benefit/risk assessment

Indinavir sulphate, the active substance of Crixivan, is one representative of the new class of protease inhibitors active against the Human Immunodeficiency Virus type 1.

The antiviral activity of the protease inhibitors results from blocking the action of the protease, an enzyme essential in viral replication. By interfering with the assembly of viral particles before release from the cell, the production of infectious viral particles is prevented. The high selectivity of this mechanism of action results in negligible inhibition of mammalian proteases.

Crixivan capsules are presented as a conventional hard gelatine capsule in both 200 and 400 mg strengths containing indinavir freebase in the form of indinavir sulphate ethanolate.

The chemical and pharmaceutical issues of the consolidated list of questions were adequately answered.

The preclinical programme was comprehensive and included relevant studies on the mechanism of specific toxicity. No outstanding preclinical questions remained.

The toxicological characterisation was in part deficient due to the difficulty in achieving high exposure in the non-rodent species and indicated that particular vigilance for unexpected adverse effects may be warranted.

The clinical benefits of Crixivan therapy have been substantiated by clinical endpoint data from two well-designed clinical studies demonstrating a substantial relative risk reduction in AIDS defining events and deaths in patients treated with IDV containing regimens. The safety profile of IDV monotherapy and IDV in combination with nucleoside analogues remains essentially unaltered. From a clinical point of view, the benefit/risk relationship is therefore considered to be beneficial.

The new strength for Crixivan (333 mg hard capsules) does not change the benefit/risk profile for Crixivan.

When reviewing the available data in children using the low strength of Crixivan (100 mg hard capsules), the efficacy of indinavir in children of 4 years of age and older has been demonstrated, but that there were still concerns on the exposure profile obtained with the recommended dosage regimen (500 mg/m² every 8 hour) with respect to efficacy and safety. However considering that there is still a medical unmet need in this population and that the antiretroviral efficacy has been demonstrated with the recommended dosage, it was decided that the benefit/risk profile of Crixivan is still favourable.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Crixivan was favourable in 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.

Medicinal Product no longer authorised