SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Invirase. 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

Composition

Capsules are supplied in amber glass bottle with a polypropylene screw closure, PVC sealing gasket and a polyurethane pad. No desiccant unit is included in the marketed pack.

Active substance

Saquinavir possesses six chiral centres resulting in 64 possible stereoisomers but only one stereoisomer is selected for the formulation intended for marketing. The synthesis of the active substance consists of a multi steps process. Following further development during the post-marketing phase, the synthesis has however been simplified to improve the efficiency of the process. The correct stereoisomeric form of saquinavir is dependent on the quality and chiral purity of the key intermediates used during the synthesis.

The impurities arising from synthesis have been well specified.

Product development and finished medicinal product

Saquinavir is characterised by low aqueous solubility, low oral bioavailability (approximately 4 %) and bitter taste. The development of the formulation intended for marketing is adequate to deal with these characteristics. Invirase is presented in a hard gelatine capsule containing micronised saquinavir mesylate and standard excipients.

Key steps of the manufacturing process (granulation, drying, batch homogeneity and capsule filling) are adequately described and validated and results of batch analysis demonstrate the consistency of the manufacturing process.

Capsules are tested according to standard methods. Analytical methods are in general well described and validated. The dissolution limit for the capsules equivalent to 75 % after 45 minutes as proposed by the applicant was considered a tight limit.

Stability

Stability results have been submitted. After storage for 12 months in glass bottles, neither physical nor chemical changes of the capsules were observed. A provisional shelf life of 2 years was therefore acceptable without any special storage conditions. Further results of the on-going stability studies of the three full-scale production batches were submitted. The presented data demonstrated a consistent quality of the product up to the new proposed shelf life of three years. Based on these data, the change to extend the shelf life from 2 to 3 years was therefore acceptable.

2. Toxico-pharmacological aspects

The genome of HIV contains the retroviral genes gag and pol, which encode structural proteins, and enzymes, which are essential for the production of mature progeny virions. The protein products of the gag and pol genes are produced initially as precursor polyproteins, which must subsequently undergo post-translational cleavage, by the virus-encoded aspartic proteinase to generate the respective structural proteins and enzymes. The enzyme responsible for this cleavage is HIV protease, it encoded by the pol gene and released from the precursor polyprotein by autoproteolysis.

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.

In contrast to inhibition of reverse transcriptase, the inhibition of the activity of HIV protease interferes with the production of viral particles also in chronically-infected cells (i.e. following integration of proviral DNA into host cell DNA).

Saquinavir is an orally active peptidomimetic inhibitor of HIV-1 and HIV-2 aspartyl proteases. Saquinavir is selective in its affinity for HIV protease and has little inhibitory activity against human aspartyl proteases.

Pharmacodynamics

Studies on pharmacodynamic effects with respect to the proposed indication

The *in vitro* antiviral activity of saquinavir was investigated in lymphoblastoid and monocytic cell lines, and in peripheral blood lymphocytes using mostly the p24 assay. Saquinavir had a potent antiviral activity against both HIV-1 and HIV-2 strains in acutely infected cells and in chronically HIV infected cells using a wide range of *in vitro* test systems. The mean values for EC50 and EC90 were 3.5 nM (range 0.75-28) for HIV-1 and 10 nM (range 0.3-200) respectively and about twice as high for HIV-2. Saquinavir demonstrated little or no effect on mammalian proteases with IC50 values higher than 10 000 nM against several human proteases. Although saquinavir metabolites, isolated from rat bile, showed a similar potency to the parent compound with regard to enzyme inhibition, the antiviral activity of all metabolites tested was very low.

In the syncytium reduction assay, the average IC90 was 21.5 nM corresponding to a free drug concentration of 0.91 nM, taking into account high binding to serum proteins. Protein binding in human plasma was found equivalent to 98 %. An average plasma concentration of 45.6 nM would have therefore to be maintained to give similar free drug concentration (0.91 nM) *in vivo*. The dosage regimen 600 mg tid for Invirase gave a maximum plasma level of 117.3 nM and a minimum of 26.1 nM. This indicated that sufficiently high levels of saquinavir can be attained in clinical therapy but also that higher doses would be appropriate to prevent low trough plasma levels.

The potential reversibility of antiviral effect was investigated. There was evidence of resumption of viral proteolysis in cells and in virions after drug removal and the time for reversal of effect appeared related to the dose of the initial exposure.

Saquinavir's cytotoxicity was low in relation to its effective antiviral activity. A therapeutic index superior than 1000 has been established *in vitro*.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Cross-resistance between saquinavir and other protease inhibitors, such as ritonavir and indinavir, is not expected to be extensive since mutations may affect protease codons other than those associated with saquinavir, i.e. G48V and L90M. No cross-resistance between saquinavir and reverse transcriptase inhibitors was found.

In order to evaluate the potential for combination therapy with reverse transcriptase inhibitors, a number of experiments were conducted to define synergy, antagonism or additivity between saquinavir and zidovudine (ZDV), zalcitabine (ddC) and didanosine (ddI). In double or triple combination studies saquinavir exhibited an additive effect on *in vitro* efficacy without enhanced cytotoxicity.

The mechanism of action of saquinavir and its antiviral effect have been demonstrated *in vitro*. The absence of *in vivo* studies was justified by the lack of properly validated animal models of HIV in animals.

Studies intended to investigate potential secondary pharmacological effects revealed limited effects on the central nervous system of saquinavir when administered orally in mice either as a single dose or daily for five days. No significant effects were observed on the cardiovascular system of conscious or anaesthetised cats neither on the gastrointestinal system. Studies investigating the effect of saquinavir on the immune system and on human platelet aggregation did not show any significant effects. However the low exposure to saquinavir in these studies limited the value of the results.

Pharmacokinetics

The pharmacokinetic profile of saquinavir was determined in several species using radiolabelled-saquinavir material and adequate methods.

The absorption after administration of a single oral dose of radiolabelled saquinavir in bile-duct cannulated rats was low (about 15 %) with corresponding low oral bioavailability (2.5 %). In all species studied, the binding of saquinavir to plasma proteins was more than 98 % and appeared to be independent of concentration. Tissue distribution was investigated in rats after a single oral dose of radiolabelled saquinavir equivalent to 10 mg/kg and an intravenous dose equivalent to 1 mg/kg. Organ/plasma ratio after intravenous administration was about 6-8 and strong binding to melanin was evident. Saquinavir crosses the brain-blood barrier to a limited extent and levels in the central nervous system was found less than 10 % of plasma levels. These results suggest that saquinavir may be less active against viruses localised in the brain. The potential passage of the placenta barrier was very low.

The metabolic profile of saquinavir in rat bile and microsomes was very similar and the metabolic profile in microsomes was comparable across all species studied. Unchanged saquinavir accounted for 20 to 50 % of circulating drug-related material but identification of the metabolites in plasma could not be performed. Metabolites characterised consisted mainly of mono- and di-hydroxylated derivatives and it was demonstrated that CYP3A4 was the major isoenzyme responsible for the biotransformation of saquinavir.

After parenteral administration in laboratory animals, it was shown that the main elimination pathway was via the bile and faeces (more than 95 %) and in rats the administered dose was almost totally recovered within 3 days. The renal elimination of saquinavir was negligible.

The pharmacokinetic profile after repeated administration was established based on toxicokinetic data obtained from the toxicology studies in rats, mice and marmosets. In rabbit and rat, the absorption and metabolism appeared saturable at medium to high doses.

Toxicology

Single dose toxicity

Acute oral toxicity studies were performed in mice, rats and marmosets and results from these studies showed that saquinavir was well tolerated.

Repeated dose toxicity

Repeated dose toxicity was studied in mice, rats, dogs and marmosets up to one year. In spite of plasma exposure approximately 7 to 40 times higher than clinical exposure, the toxicity profile of saquinavir in animals could not be clearly or consistently identified. The toxicological findings in oral studies were mild and often transient, reversible, inconsistent in nature and were in general not accompanied by histological changes.

Functional evidence of hepatotoxicity, increases in serum amino transferases, alkaline phosphatases and isocitric dehydrogenase was noted in rats and in high-dose groups of marmosets and dogs. A potential hepatotoxicity of saquinavir cannot be excluded at high exposure levels.

Saquinavir was shown to accumulate in the uveal tract of pigmented rats, indicative of binding to melanin, but the potential for phototoxic and photoallergenic reactions is considered low. No oculotoxicity was reported in repeated dose toxicity studies.

A study was performed in mice to evaluate the toxicity profile of saquinavir in combination with ZDV. The combination did not affect the characteristic haematological toxicity of ZDV or produce any new unexpected sign of toxicity. The combination of saquinavir and ddC was not investigated.

A special study was carried out in rats aged between 4 days and 9 weeks. After oral administration of saquinavir an increased susceptibility and increased mortality probably due to gastrointestinal changes was observed. These adverse effects resulted probably from to local irritancy of the compound following oral administration of suspensions of high concentration in the immature intestines. This finding indicates that a risk of intestinal disturbances cannot be excluded if saquinavir is administered to neonates in the clinical setting.

Reproduction toxicology

Results obtained from a complete programme of reproductive studies indicated that saquinavir was not associated with any reproductive, teratogenic, or developmental effects in rats and rabbits. Systemic exposure in these studies was 1.5 to 5 times higher than clinical exposure. During the post-marketing surveillance, congenital malformations, birth defects and other disorders (without a congenital malformation) have been reported rarely when pregnant women who had received saquinavir in combination with other antiretroviral agents. The actual frequency of congenital defects possibly related to saquinavir therapy is currently unknown. Appropriate wording has been included in the product information to recommend the use of saquinavir during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The secretion of saquinavir in milk has not been investigated.

The genotoxic potential has been investigated throughout a conventional battery of tests. There was no evidence of mutagenic and clastogenic potential in any of these tests.

Carcinogenicity studies performed in rodents did not evidence any carcinogenic potential of saquinavir.

Local tolerance

Saquinavir did not induce a delayed type of hypersensitivity reaction in guinea pigs. No skin irritation or corrosion was observed when saquinavir was applied on the intact skin of the rabbit.

Environmental risk

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

3. Clinical aspects

Cytotoxicity or inhibition of human proteinases occurs at concentrations 1000-fold higher than concentrations associated with antiviral activity indicating a large therapeutic index.

The effective antiviral concentration in human plasma was determined to be twice as high as the *in vitro* concentration, taking into account differences in protein binding. At plasma levels over 35 ng/ml the unbound drug concentration is expected to be higher than the IC50 in the syncytium reduction assay.

Clinical pharmacology

The pharmacokinetics of saquinavir have been characterised in 21 studies involving 363 healthy volunteers and 5 therapeutic studies with 270 HIV-infected patients. Plasma concentration of saquinavir was measured using either a well-described and adequately validated radioimmunoassay method or a liquid chromatography method with detection by ultra-violet or by mass spectrometry.

After single oral administration of saquinavir, the absorption was defined as low, highly variable and greatly affected by food. The absolute bioavailability averaged 4 % for an oral dose equivalent to 600 mg [3,8 % for saquinavir capsule and 4 % for oral suspension: coefficient of variation (CV) 73 %, range: 1 % to 9 %]. The low bioavailability seemed to be related to an incomplete absorption and an extensive first pass metabolism, although the reason has not yet been elucidated. It was observed that in healthy volunteers the extent of absorption is substantially increased by food, with an increase in AUC_{o-8} from 24 ng.h/ml following a single 600 mg dose under fasting conditions to 384 ng.h/ml when given 2 h after food. An increase of C_{max} was also measured from 3 ng/ml to 173 ng/ml respectively. Since the effect of food was shown to persist up to 2 hours, appropriate guidance was introduced to the Summary of Product Characteristics (SPC). Mechanisms by which food improves the bioavailability of saquinavir have not been clearly defined. There are too limited data to evaluate the impact of diarrhoea on the bioavailability and /or pharmacokinetics of saquinavir. It is therefore not definitely known whether patients with such conditions could receive subtherapeutic levels.

The mean steady-state volume of distribution following intravenous administration of 12 mg dose of saquinavir was estimated to be approximately 700 litres (CV 39 %). The erythrocyte/plasma ratio

(0.12) suggested a low penetration of saquinavir into erythrocytes. Limited data obtained from two patients indicated that saquinavir is present in extremely low concentrations in the cerebrospinal fluid.

Saquinavir was highly bound to plasma proteins, approximately 98 %, which was independent to concentration over the range 15-700 ng/ml. The nature of proteins involved is unknown. Displacement of saquinavir from plasma proteins is unlikely to affect the unbound concentration of saquinavir given its pharmacokinetic properties.

Systemic clearance of saquinavir was found to be high and constant after intravenous doses ranging from 6 to 72 mg. It was estimated to 1.14 l/h/kg (CV 12 %), which is slightly above the hepatic plasma flow. The mean residence time of saquinavir was 7 hours after i.v. administration to 8 volunteers.

The investigation of the metabolism using radioactive saquinavir revealed that the metabolite profiles are similar across species. Based on *in vitro* studies, saquinavir is rapidly metabolised to a range of mono- and di-hydroxylated via the cytochrome P450 system, mostly by the isoenzyme CYP3A4 (90 %). The metabolites formed seemed to have a very low antiviral activity. *In vitro* studies have shown that the metabolism of saquinavir was saturable at concentrations greater than 2 µg/ml. The route of elimination is extensively hepatobiliary. In a mass balance study, after an oral administration of 600 mg of radioactive saquinavir (n = 8), 88 % and 1 % of the dose was recovered in faeces and urine respectively within 4 days of dosing. In an additional four subjects administered 10.5 mg of radioactive saquinavir intravenously, 81 % and 3 % of the radioactivity was recovered in faeces and urine respectively, within 4 days of dosing. In mass balance studies, 13 % of circulating saquinavir in plasma was present as unchanged drug after oral administration and the remainder present as metabolites compared to 66 % after an intravenous administration. The large difference in plasma levels of total radioactivity and parent drug after oral administration supported therefore the existence of a high first pass metabolism.

After multiple oral administration of saquinavir corresponding to total daily doses ranging from 75 to 1800 mg, exposure, as evaluated by AUC and C_{max}, increased in a greater manner than dose proportional following increasing doses. This non-linearity may be a result of a saturation of the first pass metabolism with increasing dose. The steady state area under the plasma concentration versus time curve (AUC) following 600 mg tid was approximately 2 to 3 fold (95 % confidence interval (CI) 1.6 to 3.8) higher than that observed after a single dose in HIV-infected patients (n = 29).

HIV-infected patients (n = 113) administered saquinavir 600 mg tid after a meal, had AUC and C_{max} values which were about twice those in healthy volunteers (n = 6) receiving the same treatment regimen. The mean AUC-8 (dose interval) value was 757.2 ng.h/ml (CV 84 %) in-patient and 359 ng.h/ml (CV 46 %) healthy volunteers and the mean C_{max} value was 253.3 ng/ml (CV 99 %) and 90.39 ng/ml (CV 49 %) respectively.

The dosing regimen 600 mg tid was shown to maintain mean plasma concentrations above the target concentration (based on *in vitro* IC90 values) for an 8-hour interval and to be well tolerated. However, approximately 30 % of the individual plasma concentration levels fell below the target concentration during the 8 hours dosing interval. The intra- and interindividual variability in pharmacokinetic parameters were very high after oral dosing. This high degree of variability was suggested to be a result of a variable absorption and first pass metabolism, and the fact that the drug is administered with food.

The pharmacokinetic profile of saquinavir was not defined in children or in patients older than 60 years. No significant gender difference has been noticed for saquinavir.

Given the limited role of the kidney in the elimination of saquinavir no significant effects were observed in patients with mild to moderate renal impairment. No data in patients with severe renal impairment are available.

In patients with mild to moderate hepatic impairment, no correlation between hepatic function and exposure to saquinavir was found and therefore it is considered that there is no need for dose adjustment. However given the lack of data in patients with more severe impairment, caution should be exercised, as increases in saquinavir levels may occur.

Considering the above-mentioned pathway for saquinavir metabolism, the potential pharmacokinetic interactions of saquinavir with drugs, which are either substrates of CYP3A4 isoenzyme or modify its

activity, were investigated. In addition, based on publications available during the post-authorisation phase, saquinavir was shown to be *in vitro* a substrate for P-glycoprotein (P-gp), as for other protease inhibitors. The exact clinical consequences of this finding are however unknown.

The main findings were as follows:

Medicinal products used in the same indication

Co-administration of saquinavir did not influence ZDV or zalcitabine pharmacokinetics and vice versa. These antiretrovirals have a different elimination pathway.

Possible interactions with other protease inhibitors have also been considered.

Co-administration of ritonavir, as a potent inhibitor of CYP3A4, with saquinavir resulted in greatly increased saquinavir plasma concentrations. Compared to steady-state AUC and C_{max} values obtained from 114 patients that received saquinavir 600 mg tid, saquinavir exposures from patients treated with a combination regimen of saquinavir 400 mg bid and ritonavir 400 mg b.i.d increased at least 17-fold and 14-fold based on AUC and C_{max}, respectively. Saquinavir has not been shown to alter the pharmacokinetics of ritonavir following single or multiple oral doses in healthy volunteers. .

Combination therapy has been investigated with various dose regimens of ritonavir and saquinavir in a variety of studies submitted by the Marketing Authorisation Holder. The dosing recommendation was mainly supported by data from pharmacokinetic studies and the observed antiviral effects in HIV infected subjects and healthy volunteers, as well as from clinical safety and efficacy, including results from an ongoing study of the combination of saquinavir/ritonavir 1000/100 mg bid.

In HIV-infected patients, Fortovase or Invirase in combination with ritonavir at doses of 1000/100 mg bid provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with Fortovase 1200 mg tid. The pharmacokinetics of saquinavir are stable during long-term treatment.

Table 1: Mean (%CV) AUC, C_{max} and C_{min} in Patients Following Multiple Dosing of Invirase and Fortovase

Treatment	N	AUCτ (ng·h/ml)	AUC_{0-24} (ng·h/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)
Invirase 600 mg tid	10	866 (62)	2,598	197 (75)	75 (82)
Fortovase 1200 mg tid	31	7,249 (85)	21,747	2,181 (74)	216 (84)
Fortovase 1000 mg bid plus ritonavir 100 mg bid*	24	19,085 (13,943-26,124)	38,170	3,344 (2,478-4,513)	433 (301-622)
Invirase 1000 mg bid plus ritonavir 100 mg bid*	24	14,607 (10,218-20,882)	29,214	2,623 (1,894-3,631)	371 (245-561)

τ = dosing interval, i.e. 8 hour for tid and 12 hour for bid dosing
C_{min} = the observed plasma concentration at the end of the dose interval
* results are mean (95% CI)

The recommended dose of Invirase and ritonavir is 1000 mg Invirase and 100 mg ritonavir bid. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse events. Co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.
Results from a collaborative study indicated that the co-administration of indinavir (800 mg q8h) and saquinavir at the single dose of 600 mg (hard gelatine capsule), 800 mg or 1200 mg (soft gelatine capsule formulation) showed an approximately 5-fold increase in the saquinavir plasma AUC. An increase of this magnitude is not expected to influence the safety profile of saquinavir. Currently the

steady state saquinavir plasma exposures in presence of indinavir are unknown. No dose adjustment of either product is therefore currently recommended.

Results from a collaborative study showed that the co-administration of nevirapine with saquinavir resulted in a mean 24% decrease in the saquinavir AUC (95 % CI, 1-42%). No change in nevirapine exposure at steady state was observed. Although the clinical relevance of this potential interaction is unclear, the co-administration of both products is however contra-indicated.

Concomitant administration of a single 1200 mg dose of Fortovase on the fourth day of multiple nelfinavir dosing (750 mg tid) to 14 HIV infected patients resulted in saquinavir AUC and C_{max} values, which were 392% and 179% higher than those seen with saquinavir alone. Concomitant administration of a single 750 mg dose of nelfinavir on the fourth day of multiple Fortovase dosing (1200 mg tid) to the same patients resulted in nelfinavir AUC values which were 18% higher than those seen with nelfinavir alone, while C_{max} values remained unchanged. Quadruple therapy, including Fortovase and nelfinavir in addition to two nucleoside reverse transcriptase inhibitors gave a more durable response (prolongation of time to virological relapse) than triple therapy with either single protease inhibitor. The regimens were generally well tolerated. However, concomitant administration of nelfinavir and Fortovase resulted in a moderate increase in the incidence of diarrhoea.

As part of the post-authorisation data submitted, it was showed that concomitant use of delavirdine (400 mg tid) and saquinavir (600 mg tid) caused a 4.5 fold increase in plasma concentrations of saquinavir, with no increase in the elimination half-life or any changes in the absorption rate. With respect to delavirdine, there appeared to be a slight decrease in the mean values of delavirdine pharmacokinetics. On the basis of these results, no dose adjustment of either drug is therefore required.

Although no specific interaction studies have been performed, the potential risk of interaction between saquinavir and efavirenz has been considered. Appropriate statements have therefore been added to the Summary of Product Characteristics.

Other medicinal products

Co-administration of rifampicin 600 mg once daily, which is an inducer of CYP3A4 activity, led to a decrease in plasma concentration of saquinavir of 80 %, which is likely to result in sub-therapeutic concentrations. A qualitatively similar effect is expected with other inducers. Results obtained from the interaction study with rifabutin (300 mg qd) revealed a decrease in saquinavir plasma concentration of 40 %. Invirase, when used as the sole protease inhibitor (without ritonavir) in a combination regimen with other antiretroviral therapy, should not be administered concurrently with rifabutin or rifampicin as co-administration results in significantly reduced plasma concentrations of saquinavir. Limited data support the use of saquinavir with rifampicin when co-administered with ritonavir.

Ketoconazole

Co-administration of ketoconazole (400 mg once daily) and Fortovase (1200 mg tid) to 12 healthy volunteers increased saquinavir exposure at steady state (day 7 of treatment) by 190% and 171%, based on AUC_{0-8} and C_{max0-8} respectively. Ketoconazole exposure was essentially unchanged (6% decrease in AUC_{0-8} and 1% increase in C_{max0-8}). No dose adjustment is required when the two drugs are co-administered for a limited time at the doses studied.

A similar increase in plasma concentration of saquinavir could occur with other compounds that are inhibitors of the CYP3A4 isoenzyme, such as e.g. fluconazole, itraconazole and miconazole. If those medicines are taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended.

Clarithromycin

Co-administration of clarithromycin (500 mg bid) with saquinavir soft gelatine capsules (1200 mg tid) resulted in a 1.8 fold increase in saquinavir plasma AUC, a 45 % increase in clarithromycin AUC and

a 24 % decrease in clarithromycin 14-OH metabolite AUC. No dosage adjustments for either drug is required when the two drugs are co-administered at the dosed studied.

Erythromycin

Concomitant administration of erythromycin (250 mg qd) and Fortovase (1200 mg tid) to 22 HIV-infected patients resulted in steady-state saquinavir AUC and C_{max} values which were 99% and 106% higher than those seen with saquinavir alone. No dose adjustment is required when the two drugs are co-administered

Midazolam

Co-administration of a single oral dose of midazolam (7.5 mg) after 3 or 5 days of Fortovase (1200 mg tid) to 12 healthy volunteers in a double-blind cross-over study, increased midazolam C_{max} to 235% and AUC to 514% of control. Saquinavir increased the elimination half-life of oral midazolam from 4.3 to 10.9 hours and the absolute bioavailability from 41% to 90%. Volunteers experienced impairment in psychomotor skills and an increase in sedative effects. Consequently the dose of oral midazolam should be greatly reduced when given with saquinavir and the combination should be used with caution. When combined with intravenous midazolam (0.05 mg/kg), saquinavir decreased the clearance of midazolam by 56% and increased its elimination half-life from 4.1 to 9.5 hours, however, only the subjective feeling to the drug effects was increased. Therefore, bolus doses of intravenous midazolam can be given in combination with Fortovase. During prolonged midazolam infusion, a total dose reduction of 50 % is recommended (see 4.4 Special warnings and special precautions for use).

Since the inhibiting effect of saquinavir may lead to increase the concentrations of astemizole or cisapride, products that have a low therapeutic margin, it was recommended to contra-indicate such co-administrations. Similarly co-administration of terfenadine (60 mg bid) and saquinavir base presented as soft gelatine capsule (1200 mg tid) resulted in a 3.7 fold increase in plasma terfenadine exposures (AUC) and a 1.2 fold increase in AUC of the acid metabolite of terfenadine. The increased levels of unmetabolised terfenadine were associated with 6 % prolongation of QTc (cardiac repolarisation), which is considered clinically relevant. Therefore it was recommended to include terfenadine as a contra-indication.

To reflect the results observed during interaction studies or post marketing surveillance, adequate descriptions and warnings have been introduced to the SPC.

Grapefruit juice

Co-administration of 600 mg saquinavir SGC and quadruple strength grapefruit juice as single administration in healthy volunteers results in 54 % (95 % CI; 9-117) increase in exposure to saquinavir. This increase, which is less than that observed with saquinavir hard capsule is not expected to be clinically relevant and therefore no dose adjustment is recommended.

St John's wort

Further to the publication of results from a clinical study in healthy volunteers showing a significant reduction of indinavir plasma concentrations when co-administered with St John's wort (*Hypericum perforatum*), the CPMP considered that this interaction was also applicable to other protease inhibitors and non nucleoside reverse transcriptase inhibitors considering the same metabolism pathway of these substances as indinavir. The interaction seems to involve two different mechanisms: an induction of the metabolism by the cytochrome P450 isoenzyme 3A4 and the P-glycoprotein transporter. Since it may result in the loss of therapeutic effect and development of resistance, it was agreed to contraindicate the use of St John's wort in patients taking protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Likewise, HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Invirase. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Invirase is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. When used with Invirase, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with

protease inhibitors. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended

During the post-marketing phase, a pharmacokinetic interaction study showed that saquinavir as a soft capsule formulation at steady state (1200 mg tid) with sildenafil (single dose 100 mg) resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. On the other hand ritonavir led to an 11-fold increase in the AUC of sildenafil.

Although specific studies have not been performed, co-administration with drugs that are mainly metabolised by CYP3A4 (e.g. calcium channel blockers, dapsone, disopyramide, quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives, carbamazepine, fentanyl, alfentanyl, alprazolam, triazolam, and nefazodone) may have elevated plasma concentrations when co-administered with saquinavir, therefore these combinations should be used with caution. Appropriate statements have therefore been added to the Summary of Product Characteristics.

Racemisation of saquinavir under physiological conditions is extremely unlikely since it would require inversion of the configuration of all stereogenic centres.

The relationship between the pharmacokinetics of saquinavir and its antiviral activity has been investigated with saquinavir monotherapy or in combination. It was shown that the improvement in biological markers (CD4 cell counts and viral load) was correlated with saquinavir exposure at steady state.

The capsules of saquinavir used during the clinical programme and the capsules intended to be marketed have been shown to be bioequivalent.

Viral resistance

HIV isolates with reduced susceptibility to saquinavir have been selected after extensive *in vitro* passage using increasing concentrations of the compound. Analysis of the protease amino acid sequence in these isolates shows substitutions at positions 48 (glycine to valine = G48V) and 90 (leucine to methionine = L90M).

The mechanism of mutation was adequately investigated. Individual mutations led to a modest decrease in sensitivity, about 2 to 10 fold, whereas double mutations led to a 20 to 100-fold sensitivity.

Phenotypic and genotypic changes in HIV isolates from patients treated with saquinavir either monotherapy or in combination were monitored during phase I/II clinical trials. Phenotypic resistance was defined as a 10-fold decrease in sensitivity (IC50) from baseline. Two viral proteinase mutations, found in treated patients, occured mostly at codon G48V and/or at codon L90M, which is consistent with preclinical observations. The incidence across studies of phenotypic and genotypic changes in the subgroups of patients studied for a period of 16-74 weeks, with a median observation time approximately of 1 year was low (38 % corresponding to 15 out of 39 patients). .

In one study, 24 clinical isolates containing G48V and/or L90M after therapy with Invirase used as a single protease inhibitor showed a geometric mean reduction of susceptibility (increase in IC_{50}) of 7.3-fold relative to baseline virus (range 1.2 to 97-fold). In another study, 32 saquinavir-naïve patients, of whom 26 were resistant to ritonavir and/or indinavir, were treated with Invirase 1000 mg in combination with ritonavir 100 mg both two times daily, efavirenz and nucleoside analogues. 19/32 were sensitive to saquinavir at baseline. HIV RNA levels below 50 copies /ml were achieved at week 24 for 58% of those patients carrying saquinavir-sensitive virus and for 25% of those carrying virus with reduced (>10 fold) sensitivity to saquinavir.

Secondary mutations (e.g. L10I/V, K20R, M36I/L, A71T, V82X) may accompany or proceed the primary resistance mutations and give rise to greater reductions in susceptibility to saquinavir.

The overall incidence of protease genotypic resistance to saquinavir observed in a cohort of 51 antiretroviral naïve subjects after a mean of 46 weeks (range 15 to 50 weeks) treatment with Fortovase 1200 mg tid in combination with 2 NRTIs was 4%.

Cross- resistance

Cross-resistance between saquinavir and reverse transcriptase inhibitors: Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of their different enzyme targets. HIV isolates resistant to zidovudine are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to zidovudine.

Cross-resistance to other protease inhibitors: In a study of virus isolates from four clinical trials with Invirase as the sole protease inhibitor, 22 virus isolates were identified as being resistant to saquinavir following treatment for 24-147 weeks. Susceptibility of each isolate was assessed to indinavir, ritonavir, nelfinavir and amprenavir. Of the isolates, 6/22 did not show cross-resistance to the other inhibitors, while 4/22 showed broad cross-resistance. The remaining 12/22 retained activity against at least one other protease inhibitor.

Cross-resistance with lopinavir is as yet undetermined in clinical isolates, although laboratory strains with substitutions at residues 10, 84 and 90 or 10, 48, 82 and 90 did not show significant reduction in susceptibility to lopinavir.

Cross-resistance from other protease inhibitors: Subjects with high level resistance to other protease inhibitors do not necessarily show cross-resistance to saquinavir. Studies of molecular clones containing resistance mutations associated with ritonavir, nelfinavir or amprenavir showed significant resistance to these individual protease inhibitors, but not in all cases to saquinavir. In a clinical study of individuals pre-treated with indinavir or ritonavir, 81% showed reduced susceptibility to indinavir and 59% to ritonavir at baseline. Of these, 40% showed reduced (>10 fold) susceptibility to saquinavir at baseline. Following 24 weeks of therapy with Invirase 1000 mg in combination with ritonavir 100 mg both two times daily, efavirenz and nucleoside analogues, the median decrease in plasma HIV-RNA was 0.9 log 10 copies/ml for patients with phenotypic resistance to saquinavir versus 1.52 log10 copies/ml for those without resistance (p=0.03). The median number of resistance mutations in the protease gene in individuals with phenotypic resistance to saquinavir was 5.5 (range 4-8), whereas it was 3 (range 0-6) in those sensitive to saquinavir (p=0.0003). However, extensive treatment of subjects with protease inhibitors after failure can lead to broad cross-resistance in a complex, dynamic process.

Hypersusceptibility to mutant virus: Some virus isolates with reduced susceptibility to other protease inhibitors can have enhanced susceptibility (hypersusceptibility) to inhibition with saquinavir, for example viruses containing the D30N substitution after nelfinavir therapy and viruses, carrying complex substitutions patterns including I50V after amprenavir therapy. Many viruses with substitutions at residue 82, commonly selected by indinavir or ritonavir therapy, either retain, or show enhanced susceptibility to saquinavir. The clinical significance of hypersusceptibility to saquinavir has not been established.

Clinical experience

At the cut-off for the submission of the dossier, a total of 920 patients [intention-to-treat (ITT) analysis] involved in 4 major double blind, multicentre, randomised phase I/II studies **(O-13328; V-13329; V-13330** and **NV-14255/ACTG229)** have been reported. In addition, an interim analysis on changes of the biological markers of one of the two ongoing phase III studies **(NV-14256)** has been included.

Two of the phase I/II trials were dose-ranging studies, up to a maximum dose equivalent to 600 mg tid in either asymptomatic, ZDV-naive patients **(study O-13328)** or in patients with advanced infections previously treated with ZDV **(study V-13329)**. Results from these studies showed a better dose-response in CD4 cell counts for saquinavir 600 mg tid monotherapy than for other doses tested. The mean change from baseline over 16 weeks (DAVG 16) in CD4 cell counts was 32 cells/mm^3 in naive patients and 18 cell/mm^3 in ZDV-experienced patients respectively. However, the optimal dose was not determined and the possible benefits of saquinavir in monotherapy were considered very limited due to the lack of antiviral effects as determined by measurements of viral load.

Study V-13330 aimed to investigate the efficacy of combination therapy (saquinavir 75/200/600 mg tid + ZDV 200 mg tid) in 92 advanced HIV-infected ZDV-naive patients (CD4 cell counts = 300 cells/mm^3) versus ZDV and saquinavir monotherapy, most of them belonging to CDC class III-

IV. The blinded treatment period of 16 weeks was followed by an extension phase and therefore the median duration of treatment was between 36 and 52 weeks.

The overall results showed that at the dose of 600 mg, saquinavir-ZDV combination achieved better increases in CD4 cell counts and viral load suppression than either of both medicinal products alone.

The combination yielded a DAVG 16 of 52 cells/mm^3 and a decrease in plasma HIV RNA (-1.1 log 10 copies/ml for DAVG16). The combination resulted also in decrease of other markers such as β2 microglobulin, p24 antigen.

The fourth phase II study **(NV-14255/ACTG 229)** was designed to compare the efficacy and tolerability of triple therapy saquinavir/ZDV/ddC at doses equivalent to 600/200/0.75 mg tid versus saquinavir/ddC and ddC/ZDV at the same regimen. The primary endpoints were changes in plasma HIV RNA as measured by PCR technique and CD4 cell counts. This trial involved 295 advanced HIV-infected, ZDV-experienced patients in the ITT analysis who had CD4 cell counts between 50 and 300 cells/mm^3. The treatment duration was 24 weeks followed by a double-blind extension for at least 12 weeks and 170 patients remained at 48 weeks for assessment of plasma HIV RNA by PCR technique.

Treatment effects on viral load and CD4 cell counts are presented in the following tables.

Viral load over time response expressed in log 10 HIV RNA

	ZDV/ddC	**saquinavir/ZDV**	**saquinavir/ZDV/ddC**
N 1	100	97	96
Baseline	4.8	4.9	4.8
DAVG 16	- 0.2	- 0.1	- 0.6
DAVG 24	- 0.2	0.0	- 0.6
N 2	36	40	40
Baseline	4.9	5.1	5.0
DAVG 16	- 0.3	- 0.1	- 0.6
DAVG 24	- 0.3	- 0.1	- 0.6
DAVG 48	- 0.2	0.0	- 0.6

1 Intent-to-treat population**; 2** patients with valid observations for all visits up to week 48; **DAVGt** mean change from baseline over t weeks.

CD4 cell counts/mm^3 over time response

	ZDV/ddC	saquinavir/ZDV	saquinavir/ZDV/ddC
N 1	100	97	96
Baseline	169	155	146
DAVG 16	4	17	30
DAVG 24	3	15	25

1 Intent-to-treat population**; DAVGt** mean change from baseline over t weeks.

The statistical analysis at the primary timepoint (week 24) showed that the triple combination was significantly superior in increasing CD4 cell counts and decreasing viral load (as measured by peripheral blood mononuclear cell cultures which was the protocol defined endpoint) when compared with the ZDV/ddC double combination. The triple combination appeared to be superior to the saquinavir/ZDV combination only for effect on viral load and approached significance in the pairwise combination for CD4 cell counts.

The efficacy of the triple combination versus the two double combinations was also evaluated on the basis of clinical endpoints. The study was however not designed to assess the statistical differences in AIDS-defining events between the three study arms.

Two confirmatory studies, both with 600 mg tid are ongoing to evaluate the long term clinical benefit of treatment with Invirase in combination with zalcitabine and/or zidovudine. The clinical benefit will be assessed in terms of both clinical endpoints (time to first AIDS-defining events and/or death) and improvement in biological markers (viral load and CD4 cell counts).

The first study **(NV14256)** involves ZDV-experienced patients (prior ZDV therapy for at least 16 weeks) who received either saquinavir/ddC combination or saquinavir or ddC monotherapy during at least 48 weeks. Of the total of 978 patients randomised, 940 were evaluable for the clinical endpoint intent-to-treat analysis (saquinavir/ddC n = 308, saquinavir n = 318 and ddC n = 314). Patients were balanced across the three treatment arms with respect to baseline viral load, baseline CD4 counts, sex, age, race and reason for discontinuing prior ZDV. The primary endpoint is time to first AIDS defining event (ADE) or death. The analysis of clinical endpoints showed that saquinavir/ddC reduced the risk for a patient of having a ADE or dying by 53 % (p = 0.0002 with logrank test) as compared with ddC monotherapy. For death alone the risk is reduced by 72 %. This corresponded to a reduction in the rate of an ADE or death from 29.4 % to 16 % over 18 months. For death alone, the rate was reduced from 8.6 % to 4.1 % over 18 months. There was no statistically significant difference neither in time to first AIDS defining event or death nor death alone between saquinavir and ddC monotherapies.

In the three treatment groups, median treatment duration was 11 to 13 months and median follow-up has been 17 months.

At the cut-off for the submission, an interim analysis on changes in biological markers was performed. Results showed a significant superiority of the combination regimen over monotherapies for both viral load as measured by RNA PCR technique and CD4 cell counts over the first 16 weeks of treatment (refer to the tables below). The response was stable and maintained over the 16-week period.

Viral load over time response expressed in log 10 plasma HIV RNA

	ddC	saquinavir 600 mg	saquinavir + ddC
N	114	124	119
Baseline	5.2	5.3	5.3
DAVG 16	- 0.3	-0.1	-0.6

CD4 cell counts/mm^3 over time response

	ddC	saquinavir 600 mg	saquinavir + ddC
N	114	124	119
Baseline	134	151	137
DAVG 16	3	10	26

A subgroup analysis revealed that patients with a baseline CD4 cell count ≥ 100 cells/mm^3 had greater benefit for reduction in viral load compared to a baseline value < 100 cells/mm^3 (p = 0.006). No influence on the improvement of CD4 cell counts in response to therapy was observed. In both strata the combination therapy was better than either monotherapy.

Final results of the study showed that over 48 weeks the saquinavir + ddC treatment group obtained the larger median decrease (-0.4 copies /ml) compared to either the saquinavir treatment group (-0.1copies/ml) or the ddC group (-0.3 copies/ml). The median change in CD4 cell counts over 48 weeks was + 20.4 cells/mm^3 in the saquinavir + ddC arm compared to –0.4 cells/mm^3 in the saquinavir monotherapy group and –6.2 cells/mm^3 in the ddC group.

Statistical analyses were performed to describe the relationship between the surrogate marker responses and the clinical outcome. Although the study was not primarily set up to address the surrogacy of biological markers viral load and CD4 cell counts for clinical endpoint outcome, the results merely indicated a positive correlation between the effects on these biological markers and clinical endpoints outcome.

The second study SV-14604 was a double blind, randomised study designed to evaluate the clinical efficacy of the triple combination saquinavir/ZDV/ddC versus ZDV/ddC and ZDV/saquinavir in antiretroviral naive patients (less than 4 months of prior ZDV therapy) with CD4 cell counts between 50-350-cells/ mm^3. A fourth treatment arm of ZDV monotherapy was discontinued; patients originally on ZDV monotherapy were switched to saquinavir/ZDV/ddC, constituting a delayed triple therapy group. Primary endpoint was time to first AIDS defining event (ADE) or death. Of the total of 3591 patients randomised, 3485 were evaluable for the ITT analysis. Median baseline CD4 across the three arms was 199-204 cells/mm^3, and median baseline HIV RNA was 5.0-5.1 $\log_{10}$ copies/ml. Median duration of study drug treatment was approximately 14 months and the median duration of follow-up for ADE and death approximately 17 months.

The absolute numbers of ADE and death in all ITT patients were as follows:

	ZDV	ZDV + ddC	saquinavir/ZDV	saquinavir/ZDV/ddC
N	653	942	935	955
At least 1 ADE	116 (17.8%)	142 (15.1%)	116 (12.4%)	76 (8.0%)
Deaths	39 (6.0%)	34 (3.6%)	31 (3.3%)	21 (2.2%)

Using different test analysis, results demonstrated a statistically significant advantage in favour of the triple combination over the double combination in reducing the risk for a patient of having an ADE or dying (p = 0.0001).

The study was not powered to detect a difference in death alone as an endpoint. An exploratory comparison of initial saquinavir + zidovudine + zalcitabine compared to the delayed triple therapy group showed superiority of initial triple therapy including saquinavir with 76 AIDS defining events or deaths on initial triple therapy versus 116 on the initial zidovudine monotherapy-delayed triple therapy regimen (p = 0.001).

The secondary objectives of this study included changes in biological markers. With respect to viral load, results showed that over 48 weeks the saquinavir + ddC + ZDV treatment group obtained the larger median decrease in area under the curve minus baseline over 48 weeks (-1.3 $\log_{10}$ copies/ml) compared to either the saquinavir/ZDV treatment group (-0.4 $\log_{10}$ copies/ml) or the ddC/ZDV group (-0.8 $\log_{10}$ copies/ml). Only a small proportion of about 25 % patients had values of viral load under the limit of detection of the PCR assay (400 copies/ml) between weeks 4 and 48. The median change in CD4 cell counts over 48 weeks was approximately + 60 cells/mm^3 in the triple combination treatment arm compared to 25.0 cells/ mm^3 in the saquinavir/ZDV group and 24.2 in the ddC/ZDV group. Although in study SV-14604 saquinavir was given only in combination with other drugs, the nature and percentages of adverse events were well comparable to those already known for this product. No unknown clinical or toxicity findings related to saquinavir were detected.

The efficacy of saquinavir in combination has not been investigated in paediatric population nor in patients with severe renal or hepatic impairment.

Safety

The safety profile of saquinavir was established on the basis of results obtained from 574 patients who received saquinavir 600 mg tid alone or in combination with ZDV or ddC.

From these studies, only one death due to cardiac failure was considered to be remotely related to saquinavir 600 mg tid treatment. The majority of adverse events leading to treatment withdrawal were related to HIV disease or associated infections. In study NV14256, the incidence of withdrawal was higher in the ddC monotherapy group due to buccal ulcerations and peripheral neuropathy (frequent serious events associated to nucleoside analogues) than in the other groups.

The most common adverse events reported across studies are related to gastrointestinal disorders including diarrhoea (37 % in saquinavir 600 mg monotherapy and combination arms), abdominal pains and nausea. Central nervous system disorders were also frequently reported, especially headache (20 %). With regard to potential hepatotoxicity, data provided revealed that there is no evidence that the combination saquinavir/ZDV/ddC is associated with an elevation of transaminases when compared respectively with ZDV or ddC monotherapy. The potential hepatotoxicity associated with saquinavir is therefore very low.

The majority of adverse events occurring were mild and the addition of saquinavir to ZDV and/or ddC did not seem to enhance the toxicities of the latter agents. Saquinavir appeared therefore to be well tolerated. The updated database includes over 4000 patients and corroborates the initial findings.

There have been reports of increased bleeding including spontaneous skin haematomas and hemarthroses in type A and B haemophiliac 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 ritonavir, saquinavir 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 of all the protease inhibitors agents.

Post-marketing data confirmed that the most frequent adverse events were related the gastro-intestinal system, the body as a whole, the skin and appendages, metabolic and nutritional disorders and the peripheral and central nervous system. The frequency of the reported adverse events was however amended. The listing of a number of new adverse events not yet reported into the Summary of Product Characteristics (pruritus, myalgia, depression, anxiety, somnolence, hepatitis allergic reaction, abnormal renal function, Stevens-Johnson syndrome and fever) was considered necessary. In addition, liver disorders have been reported when ritonavir is administered with saquinavir.

In cases of mild impairment no initial dosage adjustment is necessary at the recommended dose. The use of Invirase (alone or in combination with ritonavir) in patients with moderate hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels may occur. There have been reports of exacerbation of chronic liver dysfunction,

including portal hypertension, in patients with underlying hepatitis B or C, cirrhosis or other underlying liver abnormalities

Following reports on adverse effects reactions related to new onset of diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus in patients receiving protease inhibitors, the CPMP agreed that appropriate statement to inform both health professionals and patients had to be included in the relevant section of the Summary of Product Characteristics and Package Leaflets of all protease inhibitor agents.

Events of special interest

Further to reports from literature and product information on the association of protease inhibitors with adverse events such as fat redistribution and other metabolic disorders, additional information were presented. These 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 are also 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 Summary of Product Characteristics of all the protease inhibitors products, and further investigation will be performed to better define this adverse event.

Increased CPK, muscle-related reactions (myalgia, myosis and rarely rhabdomyolysis) have been reported with protease inhibitors. Although it was difficult to determine the 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 according to the agreed class labelling.

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.

POST-MARKETING STUDIES OF SPECIAL INTEREST

The ***MaxCmin1*** trial was designed as an open-label study to assess whether the two protease inhibitors (PIs) indinavir 800 mg twice daily and saquinavir 1000 mg twice daily (both in combination with

ritonavir 100 mg twice daily) have differences in virological efficacy and toxicity among HIV-1 infected adult patients with a clinical need for a ritonavir-boosted PI treatment. All subjects also received at least two (non) nucleoside reverse transcriptase analogues (NRTIs/NNRTIs).

Enrolled subjects were both protease inhibitor treatment naïve- and experienced. In approximately 6 months, the trial enrolled 317 subjects of which 306 initiated the assigned treatment. Subjects were enrolled from 28 sites in 13 countries in Europe, South and North America. All subjects were followed for the duration of the trial (48 weeks). The median HIV-RNA plasma level was 10,000 copies/ml, and 40% had less than 400 copies/ml at baseline. Nadir CD4+ cell count was 110 10^6/l (median). Thirty per cent of subjects had had a previous clinical AIDS defining disease.

The primary efficacy analysis, incidence of virological failure, including all subjects that took at least one dose of the study medication (ITT/exposed population), showed no difference between the study two arms (hazard ratio of indinavir/ritonavir versus saquinavir/ritonavir: 1.0 (95% confidence intervals: 0.7-1.6). This was also the case in the on treatment analysis including all subjects that remained on the study medication (1.2 (0.6-2.4)). In the analysis where switch from the assigned treatment was counted as virological failure (ITT/e/s = failure), more failures were seen among subjects in the indinavir/ritonavir arm compared to the saquinavir/ritonavir (1.6 (1.1-2.2)). This difference was due to more switches from the assigned treatment in the indinavir/ritonavir arm (64/158 (40%) subjects versus 40/148 (27%) subjects in the saquinavir/ritonavir arm; p=0.01)). The primary reason for switch was non-fatal clinical adverse events.

A total of 100 patients developed at least one adverse event of grade 3 and/or 4 – 65/158 (41%) in the indinavir/ritonavir arm versus 35/148 (24%) in the saquinavir/ritonavir arm (p=0.002).

In conclusion, saquinavir/ritonavir had a more favourable toxicity profile and comparable antiviral effects to indinavir/ritonavir in the doses studied. More subjects in the saquinavir/ritonavir arm remained virologically suppressed on the study drug at Week 48 – probably because of a better toxicity profile.

The ***MaxCmin2*** trial was a phase IV randomised, open label, multi-centre trial, which was designed to assess whether the two protease inhibitors (PIs), lopinavir 400 mg twice daily and saquinavir 1000 mg soft capsules twice daily (both in combination with ritonavir 100 mg twice daily), have equal virological efficacy and toxicity among HIV-1 infected adult subjects with a clinical need for a ritonavir-boosted PI treatment. All subjects also received at least two (non) nucleoside reverse transcriptase analogues (NRTIs/NNRTIs).

Enrolled subjects were both protease inhibitor treatment naïve- and experienced in order to reflect the average outpatient clinic population. In approximately 6 months, the trial enrolled 339 subjects (167 on lopinavir/ritonavir, 172 on saquinavir/ritonavir) of which 324 (163 on lopinavir/ritonavir, 161 on saquinavir/ritonavir) initiated the assigned treatment. Subjects were enrolled from 36 sites in 12 countries in Europe, South and North America.

The intention was that all subjects were followed for the duration of the trial (48 weeks). At baseline the median HIV-RNA plasma level was 4.6 $\log_{10}$ (approximately 40,000) copies/ml, and 21% had less than 400 copies/ml. Median nadir CD4+ cell count was 101 10^6/l. Thirty-one percent of subjects had a previous clinical AIDS defining disease. 33 % of the study population was antiretroviral treatment naïve, and 48 % of the study population had not previously been exposed to PIs. None of the subjects in the lopinavir/ritonavir arm had been exposed to lopinavir prior to randomisation whereas 16 of the subjects in the saquinavir/ritonavir arm had previously been exposed to saquinavir.

In the primary efficacy analysis, incidence of virological failure, including all subjects that took at least one dose of the study medication (ITT/exposed population), fewer failures (29) were observed in the lopinavir/ritonavir arm as compared to saquinavir/ritonavir arm (53 failures; hazard ratio (HR) of lopinavir/ritonavir versus saquinavir/ritonavir: 0.5 (95% confidence intervals (CI): 0.3-0.8). Comparable findings were made in the analysis where discontinuation (d) of the assigned treatment was counted as virological failure (ITT/e/d = failure; lopinavir/ritonavir: 40 subjects; saquinavir/ritonavir: 63 subjects: HR: 0.6 (95% CI: 0.4-0.9)). In this analysis the better outcome in the

lopinavir/ritonavir arm was associated with a reduced risk of discontinuation of the assigned treatment due to factors not linked to antiviral activity: The treatment was stopped by 12 patients in the lopinavir/ritonavir arm, but by 24 patients in the saquinavir/ritonavir arm.

In the on treatment analysis including all subjects that remained on the study medication no significant difference was observed between the two study arms (HR 0.8 (95 % CI: 0.5-1.4, p = 0.48)). The proportion of subjects with HIV-RNA below 50 copies/ml at Week 48 (ITT/e) was 65% in the lopinavir/ritonavir arm and 57% in the saquinavir/ritonavir arm, respectively.
More subjects in the saquinavir/ritonavir arm prematurely discontinued the assigned treatment (30%, lopinavir/ritonavir: 14%, p = 0.001). The primary reasons for premature discontinuation was non-fatal adverse events (lopinavir/ritonavir: 12/163; saquinavir/ritonavir: 21/161 , p=0.09) and subject's choice (lopinavir/ritonavir: 7/163; saquinavir/ritonavir: 8/161). A total of 74 subjects developed at least one adverse event of grade 3 and/or 4 without difference between the study arms – 38/163 in the lopinavir/ritonavir arm versus 36/161 in the saquinavir/ritonavir arm.

Adjustment for protocol confounders such as subjects with and without prior PI treatment did not substantially alter the unadjusted ratios for comparing the outcome in the lopinavir/ritonavir arm relative to the saquinavir/ritonavir arm.

In conclusion, the primary finding of differences in efficacy between the two treatment arms is most likely not explained by differences in intrinsic potency or in risk of severe toxicity but rather by differences in subjective tolerability and desire to adhere to the assigned treatment.

4. Overall conclusions and benefit/risk assessment

Saquinavir was the first representative of the protease inhibitors class seeking a marketing authorisation for the treatment of HIV infected patients.
Although additional information was to be submitted with regard to chemical and pharmaceutical aspects, the data submitted were acceptable to ensure the quality and the consistency of the capsules.

The preclinical efficacy and safety of saquinavir has been adequately investigated and data generated in the studies did not give significant concerns for the clinical use of saquinavir.

During the review process it was considered that, on the basis of the contemporary efficacy and safety data available, the provisional overall benefit/risk ratio for Invirase was favourable as combination therapy. Consequently a favourable opinion for granting a marketing authorisation under exceptional circumstances was provided for Invirase capsules 200 mg. The approved indication was the following: Invirase in combination with antiretroviral nucleoside analogues is indicated for the treatment of HIV-1 infected adult patients. This opinion was based on the beneficial effect of 600 mg of Invirase administered three times daily in combination therapy with ddC in patients with advanced HIV disease, as measured by clinical endpoints including a decrease in mortality and disease progression. Moreover, the combination with ZDV in ZDV-naive patients showed a sustained impact on viral load in serum.

The provision of the final reports on the confirmatory trials was part of the specific obligations to be fulfilled by the MAH. On the basis of the data submitted throughout the year, in particularly results from the two clinical studies SV-14604 and NV-14256, the clinical benefit of saquinavir, as hard gelatine capsules, in combination therapy was confirmed as well as its tolerability. The effects of saquinavir on biological markers were rather modest in both trials. The CPMP considered appropriate to include a warning related to the risk of undertreatment with saquinavir in view of the limited and/or variable bioavailability and that saquinavir soft capsules should be used when initiation of saquinavir therapy is considered. Since the granting of the Marketing Authorisation for Invirase, new adverse events have been reported and new pharmacokinetic interactions identified. Overall, there was no indication that the risk/benefit profile is changed for saquinavir. The proposal to amend the indication related to the replacement of "nucleosides analogues" by "other antiretroviral medicinal products" was acceptable since the protease inhibitors are not only combined with nucleoside analogues but also with other protease inhibitors. Supporting literature on several examples concerning saquinavir used in combination with protease inhibitors have been submitted. Further data

support its use at 1000mg two times daily in combination with ritonavir 100mg two times daily and with other antiretroviral agents.

The approved indication for Invirase 200 mg hard capsules has therefore been changed into:

"Invirase is indicated for treatment of HIV-1 infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products..

In addition, the CHMP considered that there were no remaining grounds to keep the Marketing Authorisation under exceptional circumstances since all the specific obligations have been fulfilled. Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Invirase remained favourable in the approved indication.