SCIENTIFIC DISCUSSION

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

Soft capsules

Lopinavir and ritonavir are dissolved in a solvent mixture of oleic acid, propylene glycol and water. The soft capsules are contained either in HDPE bottles capped with child resistant, tamper evident, polypropylene closure or in clear polychlorotrifluoroethylene/PVC blisters with push through aluminium lid sock. Information has been provided in the dossier demonstrating that the oleic acid used in the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. During the clinical trials, in addition to the formulation intended for the market, two different soft capsule formulations containing lopinavir in ethanol or propylene glycol have been used in co-administration of the commercial ritonavir product.

Oral solution

Lopinavir and ritonavir are dissolved in a solvent mixture of ethanol, propylene glycol and water. The oral solution contains 42 % w/w alcohol. There was some concern with the amount of ethanol and propylene glycol especially since the oral solution is intended for use in children Adequate warnings has therefore be added in the SPC. The solution is filled into amber polyethylene terephthalate bottles and capped with child resistant, tamper evident polypropylene closures. A calibrated oral dosing syringe of 5 ml is supplied in each pack.

The formulation intended for marketing is the same as the one used in the paediatric clinical study.

As further discussed in Part IV of this document, the soft capsules and the oral solution are bioequivalent under non-fasting conditions.

Active substances

Lopinavir is the active substance within the product since ritonavir is added as the pharmacokinetic enhancer. Both substances are structurally related with respect to the core (i.e. both *S, S, S, S*-configuration) although the differences exist in the other parts of the molecules (the "wings").

Lopinavir

Lopinavir is hygroscopic, practically insoluble in water but freely soluble in a number of organic solvents. It is stable under normal storage conditions but degrades under UV light. The polymorphism aspect of lopinavir has been well studied. Lopinavir exists in an amorphous form and 4 different crystalline forms. The commercial form is a mixture of amorphous form and type I crystals. Lopinavir possesses 4 chiral centres, but the synthetic route has been tailored to be stereoselective leading to the formation of the *S, S, S, and S* enantiomer. The purity of the active substance is controlled through the purity of the intermediates of the synthesis.

The synthesis of lopinavir is a four steps convergent assembly of three starting materials. The potential impurities have been adequately studied.

Batch analyses for 33 batches (3 from Abbott Chicago and 30 from Abbott Italy) manufactured using the commercial process meet the proposed specifications.

A retest period of 18 months is supported by the stability data provided up to 18 months at 25°C/60 % RH and 6 months storage at 40°C/75 % RH. Long-term stability data will be provided when available.

Ritonavir

Ritonavir is a chiral molecule. The enantiomeric purity of the active substance is ensured by the stereoselectivity of the synthetic route and by an adequate control of the starting materials. Two polymorphs of ritonavir referred to, as Forms I and II are known. Form II is the most thermodynamically stable but is much less soluble than Form I. To prepare the formulation, the physico-chemical characteristics of Form II have to be considered.

Ritonavir used in the combination has the same origin, the same manufacturing process and the same impurity profile as the one already authorised as an individual compound and marketed in the European Union. Based on the data provided on the specifications, manufacturing process and impurities profile, the quality of ritonavir is considered acceptable. The storage of ritonavir is 2 years when stored under normal conditions.

Other ingredients

Most of the ingredients entering in the composition of the soft capsules and oral solution are described in the European Pharmacopoeia (e.g. oleic acid, propylene glycol, ethanol, castor oil polyoxyl 35) or USP standard (e.g: lecithin). The proposed acceptance criteria for the non-pharmacopeial ingredients were accepted (anhydrised liquid sorbitol-glycerol bend, colorants and flavours).

The packaging materials are standard and therefore the information provided is considered sufficient. A calibrated 5 ml dosing syringe, CE marked is included in the packaging.

Product development and finished product

Soft capsules

During the development of the formulation, the following characteristics had to be considered: poor aqueous solubility, lack of bioavailability of lopinavir and ritonavir and existence of polymorphic Form II of ritonavir. The formulation has been developed on the commercial formulation of ritonavir. No formal compatibility studies were performed but compatibility between lopinavir and ritonavir was demonstrated based on stability data observed with the two dosage forms.

Different co-formulated capsules using different ratios of the two substances dissolved in an alcohol solvent system were manufactured. The co-formulated capsule (propylene glycol system) was bioequivalent to the individual capsules formulations (ethanol) under non-fasting conditions. The choice of the excipients, solvents and enhancers to optimise the co-formulation has been adequately justified based on bioavailability studies. Due to the loss of propylene glycol during storage, a worst-case scenario has been simulating, but no crystallisation of ritonavir appeared despite of supersaturation. Due to instability of ritonavir in the formulation, capsules must however be kept at 5°C.

The manufacturing process of the soft capsules is a standard one and consists of the preparation of the solution of lopinavir and ritonavir in the co-solvent system, filling into capsules and drying. All the steps are conducted at temperatures ensuring that all the ingredients, especially ritonavir potential Form II, are adequately dissolved. The in-process controls are satisfactory and key manufacturing parameters have been studied. The validation data on 4 semi production scale batches showed that the manufacturing process produces a uniform and homogenous product that will consistently meet the specifications proposed for the finished product.

The proposed specifications and the proposed analytical validations are adequate. Results from batch analysis carried out on 15 batches confirmed satisfactory uniformity of the soft capsules at release, and indicate reliable and consistent performance of the product in clinical use.

Oral solution

The pharmaceutical development of the oral solution benefits from the one of the soft capsule. The pH for maximum ritonavir stability (~ 3) and the bitter taste of the two active substances had to be taken on board. As for the capsules, the choice of the excipients, solvents and enhancers, has been well justified based on bioavailability studies. Considering the amount of ethanol in the solution, the solution is self preservative. This has been confirmed by an efficacy preservative test for which data

has been submitted. The reproducibility of the dosing device and the compatibility between container and content were adequately demonstrated.

The manufacturing process of the oral solution is also a standard one and consists of dissolution, filtration and bottle filling. The in-process controls are satisfactory and key manufacturing parameters have been studied. The validation of the manufacturing process performed on 3 full-scale production batches has been adequately performed to ensure the reproducibility of the process.

The proposed specifications and the proposed analytical validations are adequate. Results from batch analysis carried out on 12 batches of various size confirmed satisfactory uniformity of the oral solution at release, and indicate reliable and consistent performance of the product in clinical use.

Stability of the product

Soft capsules

Data up to 12 months at 5°C and 6 months at 25°C/60 % RH on 4 batches stored in HDPE bottles and on 3 batches stored in blister packs were available. Supportive data are obtained from stability studies conducted on 3 lots stored in bulk containers at 5°C.

The results are within the specifications and no crystallisation of ritonavir Form II was identified from capsules containing the current proposed amount of propylene glycol at expiry. Based on the provided data, 18 months shelf life has been granted for the soft capsules when stored within their container at 5°C with the option for room temperature storage after dispensing to the patients for up to 42 days. The stability testing is ongoing and long-term stability data for the soft capsules will be provided when available.

Oral solution

Data up to 12 months at 5°C and 6 months at 25°C are available. Based on the preliminary data, 18 months shelf life is acceptable when the oral solution is stored within its container at 5°C, with the option for room temperature storage after dispensing to the patients for up to 42 days. Stability testing is ongoing and long-term stability data for the oral solution will be provided when available**.**

2. Toxico-pharmacological aspects

Pharmacodynamics

Lopinavir is a new peptidomimetic inhibitor of HIV protease enzyme. It blocks the ability of the viral protease to cleave precursor polyproteins necessary for viral replication.

Antiviral activity

The affinity of lopinavir to the wild type HIV protease is 0.0010 nM and ranged from 0.0022 nM to 0.0030 nM in mutant HIV protease associated with resistance to ritonavir. Lopinavir inhibits human's aspartic proteases at concentrations greater than 200,000 fold.

The *in vitro* antiviral activity of lopinavir evaluated in acutely infected lymphoblastic cell lines showed that in the absence of human serum, the mean EC_{50} of lopinavir (50 % effective concentration) against five different HIV-1 laboratory strains was 19 nM whereas in the presence of 50 % of the human serum EC_{50} was 163 nM. In the absence and presence of 50 % human serum, the mean EC_{50} of lopinavir against HIV-1_{IIIB} in MT4 cells was 17 nM and 102 nM, respectively (58 and 1044 nM for ritonavir). In the absence of human serum, the mean EC_{50} of lopinavir was 6.5 nM against several wild type HIV-1 clinical isolates in PBMC. This compares well with currently available data for other protease inhibitors (ritonavir 22 nM; indinavir 14 nM and saquinavir 3.5 nM).

Lopinavir demonstrated also antiviral activity against one laboratory strain HIV-2 with EC_{50} values of 25 and 104 nM in the absence or presence of 50 % human serum respectively.

The concentration of inhibitor which gave 50 % cytotoxic effect was about 22 µM for lopinavir in the absence of human serum and > 100 µM in the presence of human serum, giving a greater than 1,000 *in vitro* selectivity index.

The antiviral activity of lopinavir has not been evaluated *in vivo*, due to the absence of adequate animal models.

Ritonavir was found to be a very potent inhibitor of the metabolism of lopinavir (Ki equal to 0.013 µM (0.009 µg/ml)). Conversely, lopinavir was found to be a very weak inhibitor of CYP3A (Ki equal to 130 µM (82 µg/ml)).

Resistance profile

Several *in vitro* studies were performed to elucidate the resistance profile of lopinavir. Also a limited number of clinical isolates was investigated.

After sequential *in vitro* passages in presence of lopinavir and ritonavir, mutations were mainly observed at positions 32 (V32I), 46 (M46I) and 84 (I84V). These mutations are often associated to resistance to other protease inhibitors. Mutations at positions 30, 48, 82 and 90 were rare, but mutation 91 (T91S) was also selected.

In clinical isolates from patients who had failed therapy with ritonavir (n = 5), a reduced susceptibility to lopinavir was demonstrated in presence of multiple strains with *in vitro* resistance to ritonavir. However EC_{50} values for lopinavir were always inferior to EC_{50} values of ritonavir, particularly in presence of mutations at positions 20, 36, 54, 82 or 36, 54, 82 (EC_{50} values between 25 and 97 nM). Lopinavir maintained an antiviral activity against highly resistant strains to ritonavir (mutations at positions 46, 63, 71, 82, 84).

Additional *in vitro* selection experiments with lopinavir alone or with low dose of ritonavir demonstrated that the susceptibility to both inhibitors decreased with successive passages irrespective whether ritonavir was present or not.

Constructed mutants with more than 5 mutations with either I84V or I50V (mutation known to be associated with reduced susceptibility to amprenavir) as a primary mutation were highly resistant to both lopinavir and ritonavir with EC_{50} values ranging from 27- to 49-fold and 9- to 72-fold, respectively. These viruses were also highly cross resistant to amprenavir (42- to 65-fold), and of intermediate resistance to indinavir and nelfinavir (ranging from 2- to 18-fold). However, all mutant clones remained susceptible to saquinavir.

The *in vitro* characterisation of phenotypic cross resistance between lopinavir and other protease inhibitors was analysed in approximately 150 clinical isolates from protease inhibitors experienced patients (VIRCO + clinical studies M97-765 and M98-957). Data suggested that lopinavir manifests cross-resistance with ritonavir and indinavir and no or few resistance to nelfinavir and saquinavir. According to the analysis of correlation with several genotypic patterns of resistance to protease inhibitor [to indinavir (10, 46, 82 and 93), saquinavir (10, 71, 84 and 90) ritonavir (10, 54 and 82) and nelfinavir (30, 88 or 10, 71, 90 and 93)] and the susceptibility to lopinavir, mutations at positions 10, 54, 71 and 82 appear to have a substantial influence in terms of decrease of susceptibility to lopinavir (x 4 IC50). However, considering the limited number of viral strains analysed, no definitive conclusions could be drawn.

General and safety pharmacology programme

There was no evidence of any effects of lopinavir/ritonavir on the central nervous system and cardiovascular effects during the pharmacodynamic studies. The choice of the ratio lopinavir/ritonavir used in the studies was however further discussed since it differed from the one intended to be marketed (2:1 instead of 4:1). In addition, since cardiac events have been observed in dogs during the 3-month toxicity study (U waves associated with prolonged PR interval and bradycardia), the applicant agreed to perform a Purkinge fibers study to further investigate the potential effect of lopinavir/ritonavir the cardiovascular system.

No specific studies were performed on the autonomous nervous system, respiratory and gastro-intestinal systems, endocrine action, immuno-pharmacological action and metabolites action. At the highest concentration tested (i.e 10 µM in the absence of serum proteins) lopinavir reduced receptor binding and ion transport (i.e binding to L-type calcium channels reduced by mean 50 %, sodium channel site 2 reduced by 62 %) and chloride ionophore by 47 %). Lopinavir did not have any effect on the K+ channels.

Pharmacokinetics

The pharmacokinetic profile of lopinavir was determined using validated testing methods in several species (rat, dog and monkey) after single and multiple dose administration.

Absorption and distribution

Lopinavir was poorly bioavailable in rats (23 %) and not bioavailable in dogs and monkeys when administered alone. In combination with ritonavir, substantial increases in both maximum plasma concentration (Cmax) and total exposure (AUCs) of both ritonavir and lopinavir were observed in mice, rats and dogs with increasing dose of the combination. For instance, after single oral dose administration of lopinavir/ritonavir (2:1) in rats (10 mg/kg lopinavir) and humans (5.7 mg/kg), ritonavir resulted in a 2-fold increase in Cmax and a 6-fold increase in AUC for the rat and a 44-fold increase in Cmax and a 182-fold increase in AUC in humans. These parameters for lopinavir increased in an approximately dose-proportional manner in mice and a less than dose-proportional manner in rats and dogs. Ritonavir concentration increased more than dose-proportionally in all species. The absolute bioavailability estimates have however not been determined due to the lack of proper intravenous formulation with the lopinavir/ritonavir. In rats plasma levels were generally higher in females than in males, which might be explained by the higher expression of CYP3A4 activity in males as no sex difference was observed in any other species. T_{max} of lopinavir in rat, dog, monkey and human ranged between 1.5 and 4.6 hours after single oral dose administration of lopinavir/ritonavir (2:1).

Orally administered lopinavir/ritonavir was widely distributed into tissues of normal and pregnant rats, with highest tissue to plasma ratios found in the liver, adrenals and thyroid. The distribution into cellular fraction of blood was minimal and the combination did not cross extensively the brain barrier, indicating a low efficacy against viruses in the central nervous system. Lopinavir/ritonavir readily distributed in the placenta, uterus and milk of rats, a finding which has been adequately addressed in the relevant section of the Summary of Product Characteristics.

Mean plasma protein binding percentages of lopinavir determined in *in vitro* studies ranged from 98.90-97.56% in mice, 99.76-95.89% in rats, 99.45-96.29% in dogs, 98.30-95.36% in monkeys, and 99.72-97.37% in humans. The extend of protein binding generally decreased with increasing concentrations in all five species. Ritonavir may have the potential to decrease the plasma protein binding of lopinavir in human plasma, but this occured only at toxicologically or clinically irrelevant levels.

Metabolism and elimination

Lopinavir was metabolised in rat, dog and human primarily by hepatic CYP3A4 isoenzymes. Radioactivity in rat and dog faeces consisted largely of unchanged parent compound after oral administration. Although there were similarities in metabolite pattern between rat, dog and human, qualitative and quantitative differences were observed. The metabolism of lopinavir was sensitive to inhibition of ritonavir, which is in accordance with the inhibition of metabolic clearance of lopinavir by ritonavir observed in the rat.

Ritonavir is known to inhibit CYP3A4, CYP2D6, and to a lesser extent CYP2C9/10 and CYP2C19. However, due to the lower dose in the combination treatment, a less potent inhibition of CYP3A4, CYP2D6, CYP2C9 and CYP2C19 was observed. Lopinavir/ritonavir was eliminated rapidly mainly by hepatobiliary processes and excreted via faeces (> 80 % of the dose). A lower clearance of lopinavir was observed in human compared with animal models after single doses administration.

The pharmacokinetic exposure of lopinavir/ritonavir following multiple administrations was assessed during the toxicity studies. The ratio lopinavir/ritonavir used in the toxicity studies deviated from the ratio in clinical dosage form (4:1). After multiple dosing, the AUC ratios of lopinavir/ritonavir decreased with increasing doses in all species. The ratios were higher in mice, rats and rabbits as compared to the ratios in dogs. Ratios in rats were higher or comparable with the ratio at maximum human therapeutic dose, but in dogs, the ratio lopinavir/ritonavir was generally lower than in the human therapeutic situation. The consequences of these differences for the adequacy of the animal toxicity studies will be further discussed.

Toxicology

A conventional toxicity programme was conducted in accordance with Good Laboratory Practices. The oral route was mostly used since it is the proposed clinical route of administration and three different formulations were used (liquid, semi-solid and soft capsules).

Most of the toxicological studies were designed to assess the effect of both compounds in combination at a ratio that was not identical to human exposure: 2/1 or 3/1 in mice, rats and dogs compared to 4/1 for the human. Very few studies were conducted with lopinavir alone due to its poor bioavailability.

Single dose toxicity: Lethal oral dose of lopinavir when given alone was greater than 2500 mg/kg. The acute NOEL ranged from 39/20 mg/kg for rats to 20/10 mg/kg for mice given the 2:1 oral combination. The combination of the two substances showed a low acute toxic potential. Clinical signs of toxicity included reduced activity, ataxia, dyspnea, salivation, and discoloration urine.

Repeat dose toxicity: Studies were performed in rodent and dogs up to 9 months using the combination lopinavir/ritonavir. Animals were exposed to the combination at a ratio of 2/1 or 3/1. Mortality and/or severe toxicity were observed with high dosage in mice (200/100 mg/kg), rats (150/100 mg kg reduced to 100/50 mg/kg) and dogs (100/50 mg/kg reduced to 70/35 mg/kg). NOAEL obtained corresponded to AUC values of 43/3 µg.h/ml (20/10 mg/kg/d) in mice, 18.8/0.6 µg.h/ml (10/5 mg/kg/d) in rats and 75/37 µg.h/ml (50/25 mg/kg/d) in dogs. Human exposure of 400-mg/100 mg bid lopinavir/ritonavir resulted in AUC values at maximum human therapeutic dose levels of approximately 180 µg.h/ml and 20 µg.h/ml for lopinavir and ritonavir respectively (exposure ratio 9:1). The safety factor was less than one for all species studied and toxic effects were observed at human exposure levels.

Overall, the target organs were liver (mice, rats and dogs), thyroid (rats only), haematological parameters (rats) and spleen and kidney (mice only). In dogs, the most sensitive indication of toxicity was gastro-intestinal distress (emesis, diarrhoea and/or loose stools), which occurred generally 1-2 hours after dosing at all dosages tested.

In rodents hepatic changes included hepatocytomegaly, multinucleated hepatocytes, single cell necrosis and/or cytoplasmic vacuolation, increases in ALT, AST, ALP or GGT but also serum cholesterol (mice and rats) and sometimes triglycerides (only mice). Increased liver weight along with cytoplasmic vacuolation, single cell necrosis, bile accumulation and cell swelling were observed in dogs receiving high doses. The hepatocellular changes seen in dogs after 3 months appeared reversible after one-month recovery period, but the occurrence of multinucleated hepatocytes and hepatocyte lysomal inclusions in rats persisted despite one-month withdrawal period. Overall, rats were more sensitive to the hepatotoxic effects than dogs.

In the three month study in dogs, cardiac changes, characterised in particular by prominent U waves associated with prolonged PR interval and bradycardia, made in the context of electrolytic disturbance, were reported in high-dose animals (100/50 mg/kg/day reduced to 70/35 mg/k/day on day 30 due to mortality). These cardiac effects were not reported in the 6-month study in which dogs were supplemented with electrolytes and exposure reached comparable levels of the combination. Cardiac effects were also not reported in the 9-month study for which the exposure was below that achieved in the 3-month study. In order to assess the possible impact of lopinavir/ritonavir on cardiovascular system, the applicant performed an uncontrolled Purkinje fibers study in dogs. Lopinavir did not significantly delay repolarization at concentrations equal to (and exceeding 10-fold) the estimated free fraction plasma levels at Cmax values observed clinically. Concentrations of 0.15 µg/ml and 1.5 µg/ml for freely available lopinavir were used. Concentrations encompassing a 100-1000 fold range were not tested. Moreover the myocardial binding and concentration is unknown. The results of this study were considered non conclusive because of the low concentrations used and absence of positive control (preferably also containing one other protease inhibitor as a control). As a post-marketing commitment, it was shown that cloned human cardiac potassium channels (HERG) were inhibited by 30% at the highest concentrations of lopinavir/ritonavir tested, corresponding to a lopinavir exposure 7-fold total and 15-fold free peak plasma levels achieved in humans at the maximum recommended therapeutic dose. In contrast, similar concentrations of lopinavir/ritonavir demonstrated no repolarisation delay in the canine cardiac Purkinje fibres. Lower concentrations of lopinavir/ritonavir did not produce significant potassium (HERG) current blockade. The clinical relevance of these

preclinical data is however unknown and thus potential cardiac effects of this product in humans cannot be ruled out.In rats, effects on blood parameters were reported in the 50/25 and 150 mg/kg/day groups however anaemia was observed only in the two high dosages males in the 6-month study. Erythrocyte morphological changes not immune-mediated were also reported. These were not observed in mice or dogs.

Increased thyroid weight with hypertrophy of follicular cells and decreased serum thyroxine concentrations were reported in rats receiving 50/25 mg/kg/day or greater but these changes were considered species specific and therefore of no clinical relevance.

To support an indication in paediatrics, the toxicity of the combination was also evaluated in neonatal (3-4 days old at the start of treatment) or juvenile rats (16 days old at start of treatment) treated with oral doses up to 40/20 mg/kg/d and 100/50 mg/kg respectively. Results indicated a similar toxicity profile between neonatal, juvenile and adult rats but neo-natal rats seemed to be less susceptible to the combination lopinavir/ritonavir.

Genotoxicity: Lopinavir alone or in combination with ritonavir did not reveal any mutagenic or clastogenic potential effect when evaluated in the standard battery of *in vitro* and *in vivo* tests.

Carcinogenicity: Two years oral carcinogenicity study of lopinavir/ritonavir combination in mice and rats were ongoing at time of Marketing Authorisation. Submission of the carcinogenicity data was part of the follow-up measures to be fulfilled post-authorisation. Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a nongenotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumourigenic findings

Reproduction Toxicity: Combination of lopinavir/ritonavir did not alter fertility parameters. In rats the combination was slightly embryotoxic (pregnancy loss, decreased foetal viability, decreased foetal body weights) at or near maternally toxic doses (lopinavir/ritonavir 100/50 mg/kg/day). No foetal malformations related to the combination were found at any dosage but an increased incidence in skeletal variations and reductions in ossification were noted in foetuses.

A similar study in rabbits administered at dosages up to 80/40 mg/kg/day did not show embryo/foetotoxicity or teratogenicity.

In the peri- and post-natal development study, the combination altered pup viability at day 4 post-partum in rats at doses that were not toxic to the dams but not at weaning (80/40 mg/kg/day).

Local Tolerance: No local tolerance study was carried out, which is acceptable considering the administration route of lopinavir/ritonavir.

Ecotoxicity/Environmental Risk Assessment: No environmental risk assessment was conducted. This was considered acceptable since lopinavir degrades under UV-light and rapid breakdown is to be expected based on the molecular structure of lopinavir/ritonavir.

Impurities/Metabolites: There was no alteration of the toxicological profile of lopinavir/ritonavir when using formulations containing high level of total impurities/degradants at levels generally 3 to 8 fold the level expected in humans.

The soft capsules and more importantly the oral solution contain high level of propylene glycol. Although it is generally considered to be of low toxicity (GRAS status), high doses could lead to toxicity, particularly in patients at risk such as children and patients with renal or hepatic impairment. Appropriate warnings have therefore been included in the Summary of Product Characteristics.

3. Clinical aspects

The clinical programme consisted of 23 pharmacokinetic studies, 3 phase I/II studies and two confirmatory clinical to support the indication of lopinavir/ritonavir in adults. In addition, a single phase I/II study was conducted to support the indication in children. All the clinical trials were performed according to GCP standards and agreed international ethical principles. The clinical programme intended to evaluate the efficacy and safety of lopinavir/ritonavir both in antiretroviral naive and single protease inhibitor experienced patients.

The approved indication is the following:

Kaletra is indicated for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents.

Most experience with Kaletra is derived from the use of the product in antiretroviral therapy naïve patients. Data in heavily pretreated protease inhibitor experienced patients are limited. There are limited data on salvage therapy of patients who have failed therapy with Kaletra.

The choice of Kaletra to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients.

Clinical Pharmacology

- Mechanism of action

Lopinavir is a protease inhibitor with a specific inhibitory activity of the viral protease of HIV-1 and HIV-2. As indicated in Part III of this document, an approximately 10-fold decrease of antiviral activity of lopinavir was observed in the laboratory experiments in presence of 50% of human serum in comparison with absence of human serum. In PBMC, EC50 of lopinavir is 6.5 nM.

For comparison EC50 for currently available data for other protease inhibitors are 20 nM for ritonavir, 14 nM for indinavir and 3.5 nM for saquinavir.

- Resistance profile

As already mentioned in Part III of this document, the *in vitro* characterisation of resistance profile revealed that the selected mutations (V32I, M46I and I84V) are different to those associated to ritonavir resistance (M36I, I54V and V82A).

Genotypic correlates of reduced phenotypic susceptibility to lopinavir in viruses selected by other PIs:

The *in vitro* antiviral activity of lopinavir was assessed against a panel of 112 clinical isolates obtained from patients failing protease inhibitors therapy (patients from studies M97-765 and M98-957). The following eleven amino acid positions in HIV protease were found to be statistically correlated with reduced *in vitro* susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC_{50} of lopinavir against these isolates with 0-3, 4-5 6-7 and 8-10 mutations at the above amino acid positions was 0.8, 2.7, 13.5 and 44.0-fold higher than the EC_{50} against the wild type, respectively. The 16 viruses that displayed > 20-fold change in susceptibility contained all mutations at positions 10, 54, 63 plus 82 and/or 84. In addition, they had a median of 3 mutations at amino acid positions 20, 24, 46, 53, 71 and 90.

Antiviral activity of lopinavir/ritonavir in patients failing single PI therapy (M97-765):

Rebound isolates from single PI-experienced patients who began lopinavir/ritonavir therapy with at most 2 of the 11 mutations associated with reduced susceptibility to lopinavir showed no evidence of increased genotypic or phenotypic resistance to lopinavir compared to baseline isolates. In general Cmin was shown to be superior to ECI50 at baseline.

Antiviral therapy in patients failing multiple PI therapy (M98-957):

The clinical relevance of reduced *in vitro* susceptibility to lopinavir was examined by assessing the virologic response to Kaletra therapy, with respect to baseline viral genotype and phenotype, in 56 patients previous failing therapy with multiple protease inhibitors. The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.6 to 96-fold higher than the EC_{50} against wild type HIV. After 24 weeks of treatment with lopinavir/ritonavir in combination with efavirenz + NRTIs, the response rate diminished in patients who had 10 to 20-fold and 20 to 40-fold reduced susceptibility to lopinavir at baseline (78 % and 67 % respectively in comparison to 93 % in patients with < 10-fold reduced susceptibility to lopinavir at baseline). A substantial response rate of 50 % was even observed among patients with baseline isolates > 40-fold reduced *in vitro* susceptibility to lopinavir. Virologic response was also related to baseline genotype. In particular a high response rate (24/25; 96 %) was observed in patients whose baseline isolates contained 5 or less of the 11 mutations associated with reduced *in vitro* susceptibility to lopinavir compared to the response rate (2/6; 33 %) observed in patients whose baseline isolates contained 8 or more mutations.

Analysis of rebound in viral load

An analysis was performed on viral isolates from 4 naïve patients from study M97-720, 10 single PI experienced patients from study M97-765 and 9 multiple PI experienced patients from study M98-957 in whom a rebound in plasma viral load occurred during lopinavir/ritonavir therapy. In antiretroviral naïve patients, no change in susceptibility to lopinavir was noted and no new mutations compared to baseline isolates were observed. In single PI experienced patients, viruses remained susceptible to lopinavir but at reduced level and new mutations associated with reduced susceptibility to lopinavir and/or resistance to other PI appeared. In one of these multiple PI experienced patients, following rebound, EC_{50} of lopinavir increased 99-fold above the wild type and four new mutations in protease region were detected. In addition all the rebound isolates were resistant to efavirenz.

To evaluate the emergence of resistance in case of failure to lopinavir/ritonavir, preliminary genotypic and phenotypic data from viral isolates obtained from antiretroviral naive patients (M98-863) experiencing viral rebound at 48 weeks were analysed. The absence of detection of any mutation is noteworthy (0/31 (0%) versus 21/64 (33%) in lopinavir/ritonavir and nelfinavir arms respectively. Furthermore, mutation M184V was detected in viral isolates from patients receiving lamivudine to a lesser extent in the lopinavir/ritonavir than nelfinavir arms (14/31 (45 %) versus 55/64 (86 %) respectively). These data are supportive of the use of the concept of "high genetic barrier" and consequently of relevance to the use of the combination in antiretroviral naive patients. However, further investigations are necessary, particularly to define optimal therapeutic strategies in case of failure to lopinavir/ritonavir.

Pharmacokinetics

The pharmacokinetic profile of lopinavir was determined in 5 pharmacokinetic studies, 9 interactions studies and 9 bioequivalence/bioavailability studies after single and multiple doses in healthy volunteers, HIV-1 infected patients and paediatric patients using adequate analytical methods. Except for the single dose study, lopinavir has always been administered with ritonavir. Various dosing schemes were used (lopinavir ranging from 100 mg to 800 mg and ritonavir ranging from 50 mg to 300 mg) to investigate the effect of ritonavir on lopinavir and to optimise the dose.

Absorption and distribution

Although the absolute bioavailability of lopinavir is unknown due to the lack of an adequate intravenous formulation, concentrations after administration of doses of 200 mg to 800 mg led to very low plasma concentrations as consequence of large presystemic metabolism. Therefore lopinavir has been developed with low dose of ritonavir since the co-administration substantially increased the plasma concentrations of lopinavir, as a consequence of inhibition of CYP3A-mediated metabolism of lopinavir by ritonavir.

After oral administration, lopinavir in combination with ritonavir was well absorbed and the relative bioavailability of lopinavir was increased by 160-fold. The amount of ^{14}C lopinavir unchanged recovered in the faeces accounted for approximately 20 %, indicating extensive absorption of lopinavir. Rate of absorption was low with mean Tmax lying between 5 to 6 h.

Lopinavir does not seem to be a substrate for the counter-transport protein P-glycoprotein (PgP), like other available protease inhibitors.

When administered alone, the increase of lopinavir plasma concentrations with dose was more than dose-proportional (doses of 200, 400 and 800 mg). With a fixed dose of ritonavir, increasing single doses of lopinavir led to an almost proportional increase in lopinavir concentrations. The pharmacokinetics of a fixed ritonavir dose was minimally affected by co-administration with different doses of lopinavir. With a fixed lopinavir dose (400 and 800 mg), increasing ritonavir dose (50 to 200 mg) led to an increase in lopinavir concentrations, although saturation occurred at higher ritonavir dose.

At therapeutic dosage (lopinavir 400 mg/ritonavir 100 mg), the following parameters were obtained:

	AUC (µg.h/ml	Cmax (µg/ml)	C12 (µg/ml)
Lopinavir	105± 34	8.5 ± 2.0	0.23 ± 0.10
Ritonavir	4.7± 1.7	0.6 ± 0.2	0.19 ± 0.09

Food increased the bioavailability of both lopinavir and ritonavir. Under fasting conditions, mean lopinavir AUC and mean C_{max} values were respectively 28-46 % and 13-32 % lower compared to the ones obtained after a moderate fat breakfast. Similarly ritonavir AUC and C_{max} were also decreased. Food intake had an even more pronounced effect on lopinavir when given as oral solution since mean AUC and C_{max} values were respectively 46-53 % and 35-39 % lower under fasting conditions. A high fat meal enhanced lopinavir and ritonavir concentrations by 25 % compared to a moderate fat meal. Whereas early phase I/II studies were performed regardless of food intake, patients in phase III studies received doses with food as recommended in the Summary of Product Characteristics.

Distribution

As no intravenous formulation is available, the total volume of distribution is unknown. However the apparent distribution volume in man was estimated to be around 40 litres, which seemed rather low. Protein binding assessed *in vitro* and *in vivo* showed that lopinavir is highly protein bound (approximately 99 %) to both human serum albumin and α1-acid glycoprotein. Distribution into cerebrospinal fluid and semen of humans is under investigation.

Metabolism and elimination

Lopinavir is eliminated mainly through oxidative metabolism. After administration of a single dose of radiolabeled lopinavir, more than 90% of the dose was recovered in urine (10 %) and faeces (83 %). Unchanged lopinavir represented about 20 % of the eliminated dose. As demonstrated *in vitro* studies, the metabolism is via cytochrome P450, mainly CYP3A4 and CYP3A5. The major metabolites present in human faeces after oral dosing were M-3/4 (10.1 % of mean total dose), M-9/10 (7.4 %) and M-11/12/13/14/15 (8.9 %). The *in vitro* antiviral activity for the metabolites is unknown except for M-1 and M3/4, which have potency comparable to that of the parent drug. Unknown metabolites represented 9 % of the administered dose. Low concentrations of metabolites were measured in plasma.

After single dose administration, mean elimination half-life (t1/2) ranged between 2 to 3 hours and seemed to be increased after multiple dose administration (about 4-6 h).

Renal clearance is a minor elimination process (Clr = 0.08 to 0.15 l/h-1.3 to 2.5 ml/min for lopinavir and 0.17 to 0.24 l/h –2.8 to 4.0 ml/min for ritonavir). Total clearance is unknown; assuming good absorption, Cl/F should be close to Clt. In healthy volunteers after single dose Cl/F = 4.4 ± 1.1 l/h (73 ml/min) and at steady state Clt was slightly increased reflecting auto-induction process [~ 6.4 ± 4.4 l/h (108 ml/min)]. Such low clearance was in agreement with the important decrease in the rate of metabolism of lopinavir in the presence of ritonavir. Clearance was reported to be higher during the day.

There was no evidence of different pharmacokinetic profile in healthy volunteers and HIV-1 infected patients. Although it has not been specifically studied, the body weight seemed to influence pharmacokinetic of lopinavir (lower AUC and Cmax) whereas gender and race did not seem to have any impact.

Multiple dose study performed in healthy volunteers showed that lopinavir pharmacokinetic is time dependant with an equilibrium of lopinavir concentrations being reached after 2 weeks and that lopinavir concentrations are dependant on ritonavir dose.

In HIV-1 infected patients, multiple dosing of lopinavir/ritonavir (400/100 mg twice daily for 3 to 4 weeks, without meal restriction) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg.h/ml. Lopinavir and ritonavir concentrations reached steady state by day 14. Pharmacokinetic parameters remained stable from weeks 3 to 24. Ctrough were well

higher than the EC_{50} against wild type viral strains, measured in the presence of 50 % human serum (64 ng/ml). However unbound concentrations were very low. The consequences on the inhibitory quotient (Ctrough/ EC_{50}) will be further discussed by the applicant.

Co (pre-morning dose) was higher than Cmin (post morning dose) as a consequence of a higher clearance during the day. The clinical consequence of this finding is however unknown.

Although ritonavir decreases variability in lopinavir concentrations by inhibiting its metabolism, the interindividual variability was high ranging between 30 and 60 % among the studies analysed.

Special population

At time of Marketing Authorisation, the pharmacokinetic profile of lopinavir/ritonavir had not been established in the elderly and patients with renal and/or hepatic dysfunction. Since lopinavir and ritonavir are eliminated mainly through biotransformation by the liver, the impact of renal impairment should be minimal. Appropriate recommendations have however been included in the Summary of Product Characteristics to reflect the lack of data. In addition, the applicant undertook to provide the results of a pharmacokinetic study in hepatic impaired patients as part of post-authorisation follow-up measures (study M01-347).

The pharmacokinetic profile of lopinavir/ritonavir in children was assessed in the subgroup of patients enrolled in Phase I/II study M98-840 (n = 53) that is described in the clinical section of this report. Patients aged 3 months to 12 years received the adult body surface area-equivalent dose of 230/57.5 mg/m^2 BID as well as the higher dose 300/75 mg/m^2 BID. The latter dose corresponded to a 30 % increase over the body surface area based adult equivalent dose. This increase was explained based on the experience in adults patients treated with lopinavir/ritonavir and ritonavir which suggested that paediatric patients may require 20 % to 30 % higher than the body surface area based equivalent adult dose in order to provide lopinavir exposure similar to the one in adults.

Children receiving nevirapine concomitantly with lopinavir/ritonavir had lower exposure assessed with AUC0-12 and Ctrough (52 $\pm$ 28 versus 73 $\pm$ 31µg.h/ml and 3.8 $\pm$ 3.6 versus 4.7 $\pm$ 2.9 µg/ml respectively at the 230/57.5 mg/m^2 BID). Lopinavir concentrations were increased with increasing dose to 300/75 mg/m^2 (Ctrough 5.6 $\pm$ 3.2 and 7.9 $\pm$ 4.5 µg/ml in children with or without nevirapine respectively). In the absence of nevirapine, the dose 230/57.5 mg/m^2 provided an adequate pharmacokinetic exposure similar to that obtained in adult patients receiving 400-mg/100 mg twice-daily regimen without nevirapine. The higher dose, without concomitant use of nevirapine provided higher exposure than in adults (approximately 150 % in terms of AUC and Cmax). Both doses were well tolerated but the dose of 230/57.5 mg/m^2 BID was selected in children, the higher dose being only recommended when lopinavir/ritonavir is associated with nevirapine. There was no analysis to evaluate whether pharmacokinetic parameters were age-related however it appears that experience in children <2 years of age is too limited to allow definitive conclusions.

Interaction studies

The pharmacokinetic interaction profile of lopinavir/ritonavir mainly depends on the interaction potential of ritonavir, which is a potent inhibitor of CYP 3A4, but its use at a lower dose in the combination could have consequences for the magnitude of the interactions. Considering that HIV infected patients are frequently subject to multiple therapies, interaction studies have been conducted with commonly co-administered medicinal products. . In addition, although lopinavir is not a P-glycoprotein substrate, the inhibitory role of lopinavir/ritonavir and its clinical relevance is currently unknown.

	Co-administered substances	Subjects	I D ose	C_{max}	AUC	Cmin	Compar-ator
Effect on Lopinavir (LPV)/ ritonavir (RTV) pharmaco-kinetics	***nevirapine***	healthy	200 mg during 14 weeks followed by 200 mg BID	no	no	no	
	efavirenz	***healthy***	600 mg QHS	No	LPV decreased by 19.2 %	LPV decrease 38.9 %	
		HIV infected	533/133 LPV/RTV	no	no	no	Historical data with 400/100 mg
	ritonavir		100 mg BID		33 %	64 %	400/100 mg
Effect of LPV/RTV on co-administered PI	***indinavir***	*healthy*	Indinavir 600 mg BID	decrease	no	increase	Historical data with 800 mg TID
	nelfinavir	*healthy*	750 mg BID	Similar or increase	Similar or increase	Similar or increase	Historical data 750 mg TID
	saquinavir	*healthy*	Soft capsules 800 mg BID	increase	increase	increase	Historical data 1200 mg TID

Although in healthy volunteers, nevirapine was not found to impair lopinavir pharmacokinetics, lopinavir concentrations were lower in HIV-1 infected paediatric patients treated with lopinavir/ritonavir concomitantly with nevirapine. The clinical relevance of the pharmacokinetic interaction is unknown and no dosage recommendation can be made. However, based on clinical experience, Kaletra dose increase to 533/133 mg (4 capsules) twice daily may be considered when co-administered with nevirapine, particularly for patients in whom reduced lopinavir susceptibility is likely.

An interaction study with efavirenz showed that an increase in lopinavir/ritonavir dose to 533/133 mg BID led to increased Cmin and exposure. However, further investigations are needed because it was suggested that this dose regimen might not be optimal for all patients, considering the high interindividual variability (Cmin 5.9 + 5.5 mg/l).

Considering the design of the interaction studies with protease inhibitors (parallel group, no control arm), results are difficult to interpret and no formal dosage adjustment can be recommended.

The applicant therefore undertook to further assess the potential interactions between lopinavir/ritonavir and currently approved protease inhibitors. Subsequently, Kaletra (400/100 mg twice daily) has been studied in combination with reduced doses of amprenavir (M01-299), indinavir (M01-340), nelfinavir (M01-341) and

saquinavir (M01-340) in steady-state controlled healthy volunteer studies. Main results of these studies have been adequately reflected in section 4.5 of the SPC. No formal pharmacokinetic studies have been performed to evaluate the potential interaction between lopinavir/ritonavir and stavudine or lamivudine. However based on the pharmacokinetic analysis of study M97-720, no change in the pharmacokinetic of lopinavir was observed when these substances were co-administered.

Other medicinal products

A relatively large decrease in ethinyl estradiol and a smaller decrease in norethindrone pharmacokinetic parameters were observed after 14 days of lopinavir/ritonavir co-administration in healthy volunteers, probably due to enzyme induction. Considering the extent of decrease in ethinyl estradiol concentrations, estrogen-based oral contraceptives should not be used as a primary method of birth control in subjects receiving lopinavir/ritonavir.

Co-administration of lopinavir/ritonavir with methadone significantly decreased the AUC and C_{max} mean values of methadone by about 50%, probably due to enzyme induction. Monitoring plasma concentrations of methadone is therefore recommended to avoid withdrawal symptoms.

Administration of lopinavir/ritonavir concurrently with ketoconazole, pravastatin or atorvastatin had no clinically significant effect on lopinavir and ritonavir pharmacokinetics. However lopinavir/ritonavir increased atorvastatin C_{max} and AUC_{24} by 4.7-fold and 5.9-fold, respectively. In addition lopinavir/ritonavir increased (about 30%) pravastatin C_{max} and AUC_{24}. Lopinavir/ritonavir increased ketoconazole AUC (3-fold), but had little effect on C_{max}.

Rifampicin co-administered with lopinavir/ritonavir significantly decreased lopinavir AUC_{12} by 75%. C_{max} decreased by 55% and C_{min} by 99% relative to lopinavir/ritonavir alone. Likewise, ritonavir AUC_{12} was decreased by 67%, C_{max} decreased by 58%. and C_{min} decreased 92%. As a consequence, the co-administration is contra-indicated.

Rifabutin did not have a clinically significant effect on lopinavir or ritonavir pharmacokinetics. Lopinavir C_{max} and AUC values were increased by < 20 % during rifabutin co-administration. In contrast, lopinavir/ritonavir co-administration had a profound effect on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. After dose-normalisation, concurrent lopinavir/ritonavir dosing increased the sum of rifabutin and its metabolite C_{max}, C_{min} and AUC values by an estimated 3.5-, 9.5- and 5.7-fold, respectively. If co-administration is clearly indicated a dose reduction of 75 % for rifabutin (i.e. 150 mg every other day or 3 times per week) is recommended. Further reduction may be necessary.

All the results from these studies have been adequately reflected in the Summary of Product Characteristics.

Further to the publication, during the post-marketing phase, 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*), it was 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.

Bioequivalence

Several formulations were used during the clinical development of lopinavir/ritonavir. The co-formulation intended for marketing was shown to be bioequivalent for lopinavir to the different formulations of soft capsules under both fasting and non-fasting conditions. The soft capsule and the oral solution are bioequivalent under non-fasting conditions.

Clinical Efficacy

The antiviral clinical efficacy was evaluated in 3 phase I/II and III clinical studies in adults, and a single phase I/II study including naive to single PI experienced children. A total of 712 adults and

paediatrics patients have been exposed to lopinavir/ritonavir. Two main studies were conducted in adults, one in antiretroviral naive and one in single PI experienced patients

Dose-response studies and Main Clinical studies

Dose response studies

Three dose range phase I/II studies were performed to explore the antiviral response to lopinavir/ritonavir at different dose levels in HIV-1 infected patients (see table below).

M97-720 **Antiretroviral naive patients**	**M97-765** **Single protease inhibitor experienced patients**	**M 98-957** **Multiple protease inhibitors experienced patients**
Group I (n = 32): Lopinavir/ritonavir 200/100 BID OR Lopinavir/ritonavir 400/100 mg BID + at Day 22 stavudine/lamivudine Group II (n = 68): enrolled after a review of 4 weeks of dosing by 16 patients in Group I : Lopinavir/ritonavir 400/100 mg BID + stavudine/lamivudine OR Lopinavir/ritonavir 400/200 mg BID + stavudine/lamivudine In group I and II doses of ABT378/r were blinded. All patients who were ongoing at Week 48 were converted from their randomised double-blind dose of lopinavir/ritonavir to open label Lopinavir/ritonavir 400/100 mg BID between Week 48 and Week 72 (beginning when amendment n°5 dated February 10, 99 was approved)	The protease inhibitor in their existing regimen was discontinued on Study Day-1. Then patients (n = 70) were randomised to receive: From Day 1 to 14 : Lopinavir/ritonavir 400/100 mg BID + preexisting NRTIs OR Lopinavir/ritonavir 400/200 mg BID + preexisting NRTIs At Day 15 : Each patient's NRTI regimen was changed to a new regimen that included at least one NRTI that the subject had not previously received. Nevirapine was added to each patient's regimen.	Arm A (n = 29): Lopinavir/ritonavir 400/100 mg BID, efavirenz (EFV) 600 mg QD plus NRTIs to be determined by the investigator. Arm B (n = 28): **Day 1 to Day 13** : Lopinavir/ritonavir 400/100 BID, EFV 600 QD, plus NRTIs to be determined by the investigator. **Day 14 onward** : Lopinavir/ritonavir 533/133 mg BID, EFV 600 QD, plus NRTIs to be determined by the investigator.

In **study M97-720**, when lopinavir/ritonavir was given alone, there were no statistically significant differences between the dose groups (mean change of plasma HIV-RNA from baseline was – 1.84 log10 copies/ml in 200/100 mg arm compared to – 1.86 log10 copies/ml in the 400 mg/100 mg arm) at week 3. The overall virological response, in terms of proportion of patients with viral load below the limit of detection (< 400 copies/ml) and the safety profile were similar between all doses

tested at week 24. The number of patients randomised was however low. At week 48, a statistically significant difference appeared in favour of 400/100 mg in the group II (on treatment analysis 100 % versus 80 %; p = 0.010), although it was unexpected according to pharmacokinetic considerations.

A final study report was submitted in post-marketing phase. Overall, 10 subjects demonstrated a loss of virologic response through week 48. A single additional subject demonstrated a loss of virologic response through Week 72. A total of 16 subjects demonstrated a loss of virological response through the end of the week 204 windows. Results of genotypic resistance testing were available from 11 of the 16 subjects who met the criteria for loss of virologic response at or prior to week 204 (in 5 subjects the results are unavailable due to a low number of viral copies). None of the 11 subjects exhibited genotypic resistance to lopinavir (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84 or 90). The absence of resistance to lopinavir was confirmed by phenotypic resistance testing. 3 of the 11 subjects demonstrated the M184V mutation I reverse transcriptase

The long term data (204 weeks) of this dose finding phase II study performed in antiretroviral naïve patients should be interpreted with caution, due to the heterogeneity of the schedule regimens received by the patients. However, they are suggestive of a durability of the virological response consistent with a limited rate of premature discontinuation at this stage and the absence of emergence of resistance.

In **study M97-765**, based on week 2 results, when lopinavir/ritonavir represented the only change of the patient regimen, the antiviral activity of lopinavir/ritonavir was significant in first line protease inhibitor experienced patients, as measured by the viral load change from baseline (approximately -1 log copies/ml). After Day 15, the addition of nevirapine and the change of at least one NRTI rendered difficult the assessment of the impact of lopinavir/ritonavir on the overall antiviral response. As for study M97-720, no difference could be demonstrated between doses tested.

In this study, the durability of the antiviral response was sustained up to 144 weeks in lopinavir/ritonavir containing regimens.

In study **M97-957**, the dose increase of lopinavir/ritonavir from 400/100 mg to 533/133 mg in case of combination with efavirenz allowed to maintain a satisfactory pharmacokinetic exposition, hence a virological response. The lopinavir Cmin values were 44 % lower in the 400-mg/100 mg arm compared to the values obtained in patients without co-administration of efavirenz. It is of interest to note that in this population (highly experienced protease inhibitors patients with significant reduction of phenotypic sensitivity to several protease inhibitors) the virological response to lopinavir/ritonavir was quite high. When considering both arms, approximately 75 % of patients had viral load < 400 copies/ml at week 24.

Overall, the proportion of patients with HIV-RNA levels <400 copies/ml (ITT/LOCF) at week 24 and 48 in the above mentioned dose-finding studies did not indicate a dose response effect. Because of the better safety profile of the 400/100 mg lopinavir/ritonavir BID dose level, this regimen was chosen for the Phase III clinical evaluations. The dose selection of 400 mg lopinavir in combination with 100 mg ritonavir was also supported from the pharmacokinetic point of view. However, the virological response results appeared to favour the 533-mg/133 mg BID lopinavir/ritonavir dose level in the presence of efavirenz, as it lowers the plasma levels of lopinavir by approximately 40%.

Relationship between pharmacokinetics-pharmacodynamics

An attempt was made to establish a relationship between concentrations and virological effect. The 400 /100 mg dose was selected as it provided C_{trough} concentration in excess of the EC_{50} corrected for the presence of plasma protein. This dosage, which provided a mean inhibitory quotient above 75 ($IQ = C_{min}/EC_{50}$) was found to be favourable with an acceptable tolerance. No dose concentration-efficacy relationships could be evidenced in protease inhibitor experienced patients (study M97-765) most likely due to this high inhibitory quotient. EC_{50} of viral isolates were highly variable ranging from < 0.1 μg/ml up to 1 μg/ml. On the other hand, in highly antiretroviral-experienced patients (study M98-957), with 100-fold differences in viral susceptibility, the IQ became a predictive variable.

Main studies

Results up to 24 weeks from two main studies in patients using the lopinavir/ritonavir at the dosage regimen 400/100 mg BID were provided in the submission of the application. The efficacy and safety

of the combination has been evaluated in antiretroviral naïve and single protease inhibitor experienced but NNRTIs naïve patients.

The overview of the main clinical studies in adults and children is displayed in the table below:

	Clinical studies in adults		**Clinical study in children**
	M98-863	**M98-888**	**M98-940 (phase I/II)**
Design	Randomised, double blind, multicentre	Randomised, open label, multicentre	Randomised, open label
Population	Antiretroviral naive patients (> 12 years) with viral load above 400 copies/ml	Antiretroviral experienced single PI experienced and NNRTI naive patients (> 12 years) with viral load of at least 1000 copies/ml	HIV infected patients between 3 months and 12 years (inclusive) with viral load above 400 copies/ml NNRTI naive
Dosage regimen	400 mg/100 mg BID versus nelfinavir 750 mg tid in combination (blinded treatment) with stavudine and lamivudine (open treatment) After week 24 patients received nelfinavir at the dose of 1250 mg bid or 750 mg tid.	400 mg/100 mg BID versus ISPI*in combination with nevirapine and 2 NRTIs (one of which had to be new)	230/57.5 mg/m^2 bid lopinavir/ritonavir versus 300/75 mg/m2 bid in combination to NRTIs in antiretroviral naive and nevirapine in antiretroviral experienced children.
Study duration	48 weeks (24 weeks results available)**	48 weeks (16 weeks available and preliminary data at 24 weeks)	48 weeks (24 weeks available)**
N enrolled	653	118	100

** ISPI =investigator selected PI used as single agent or dual PI regimen*

*** Preliminary data were presented to the CPMP in response to the concern raised on the long-term efficacy of lopinavir/ritonavir in antiretroviral naive patients.*

Primary endpoints/assays

The primary endpoints were the proportion of patients with plasma HIV RNA levels below the limit of quantification (< 400 copies/ml) at week 24 and time until loss of virologic response through week 48. Time until loss of virologic response was defined as the first occurrence of any of the following events provided the patient had achieved an HIV RNA level below 400 copies/ml at week 24: 2 consecutive viral load measurements above 400 copies/ml; addition of a new antiretroviral agent; treatment-related premature discontinuation from the study.

Statistical analysis

Study M98-863 was designed as an equivalence study between two highly active antiretroviral therapies. The sample size of approximately 330 patients per arm was calculated to provide 80 % power to determine that lopinavir/ritonavir arm was equivalent to nelfinavir arm in the week 24 analyses using a tolerance limit of 10 %. The sample size was calculated to detect a difference of at least 10 %.

In study M98-888, the planned sample size of 150 per treatment group was designed to provide sufficient power to determine equivalence and to detect a difference of at least 16% between the treatment groups at week 24.

For both studies, results are presented using the intent-to-treat analysis with missing data equal failure and last-observation carried forward. On treatment analysis, which includes all observed data while patients were on assigned treatment, has also been performed (missing values were excluded from the analysis, as were values obtained while treatment has been interrupted for at least 3 days).

Results

The baseline characteristics of the studies are displayed in the table below:

	Clinical studies in adults		**Clinical study in children**
	M98-863	**M98-888**	**M98-940**
N included in the efficacy levels	326 in the treatment group and 327 in comparative group	118 (at 16 week) and 50 (24-26) at 24 weeks	100
Sex	Male 80 %; Female 20 %	Male (90 %)/Female (10 %)	Female 57 %
Mean age	37.8 (19-84)	40.7 (18-71)	5.3 (range 6 months to ~ 12 years)
Mean baseline CD4	257.5-260.2 cells/µl	323 cells/ µl	2.78 log 10 cells/µl
Mean baseline viral load	~ 4.9 log 10 copies/ml	~ 4.0 log10 copies/ml	4.68 log10 copies/ml
Mean time with diagnosis of HIV (years)	2.3 (0.0-16.7 years)	6.5 years (0.9 – 17.1)	~ 3.1 (0.0 – 10.5)

Patients were mainly Caucasians. No data was provided regarding CDC stage of patients at baseline. In study M98-888, patients were mainly experienced with nelfinavir and indinavir, however the duration of prior exposition to protease inhibitor is unknown.

In the paediatric study, among 100 children enrolled, 14 were less than 2 years of age and 56 were antiretroviral experienced patients, of those 24 were protease inhibitor experienced children.

Efficacy results

Study M98-863

This is a well designed, double blind study performed on a large sample size aiming to compare a tri-therapy including the fixed combination lopinavir/ritonavir with a standard tri-therapy including nelfinavir in treatment naive patients. This study is still ongoing but 24 weeks data were presented.

Overall there was 11 % of premature discontinuation at week 24 (36 in the treatment arm versus 38 in the comparator). There were mainly due to lost of follow-up and adverse events related to HIV infection.

Proportion of patients with undetectable viral load (< 400 copies/ml) at Week 24

Treatment Arm	**ABT-378/r**	**NFV**	**p value comparing treatment arms**
On treatment	254/277 (92%)	232/285 (81%)	<0.001
ITT (NC=F)	259/326 (79%)	233/327 (71%)	0.015
ITT (M=F)	259/326 (79%)	233/327 (71%)	0.015

ITT: intent-to-treat; M=F: missing = failure; NC = F: non completer = failure; LOCF: last observation carried forward.

On treatment: includes all observed data while subjects were on assigned treatment. Missing values were excluded from the analysis, as were values obtained while treatment has been interrupted for at least 3 days.

Whatever the population analysed, the results were more favourable in the lopinavir/ritonavir arm compared to the nelfinavir arm. According to the predefined criteria, both treatment arms should be considered as equivalent if the lower limit of the confidence interval at 95 % was between –10 % and 0. In the ITT (NC = F), the 95 % confidence interval of the difference indicated the superiority of combination over the comparator arm. The time of reaching undetectable levels of virus was not significantly different between both treatment arms.

A subgroup analysis showed that effects of lopinavir/ritonavir were more favourable in patients with high viral load (> 100,000 copies/ml) and in patients with CD4 cell counts < 50 cells/mm^3 at baseline.

Proportion of patients with undetectable viral load (< 50 copies/ml) at Week 24

	Number of patients with HIV RNA levels < 50 copies/ml ; (n/N, %)		
Analysis	**LPV/RTV (N = 326)**	**NFV (N = 327)**	**P-value[a]**
ITT (M=F)	211/326 (65 %)	197/327 (60 %)	0.237
ITT (LOCF)	211/326 (65 %)	197/327 (60 %)	0.237
On treatment	207/275 (75 %)	196/278 (71%)	0.207

ITT: intent-to-treat; M=F: missing = failure; LOCF: last observation carried forward.

On treatment: includes all observed data while subjects were on assigned treatment. Missing values were excluded from the analysis, as were values obtained while treatment has been interrupted for at least 3 days.

As displayed in the table, the difference between both arms was not statistically different when using the ultrasensitive test.

In terms of viral change from baseline, the mean decrease from baseline to week 24 was 2.20-log10 copies/ml for the lopinavir/ritonavir group and 2.11 log10 copies/ml for the nelfinavir group.

There was no statistically significant difference between treatment groups with respect to mean change from baseline to week 24 for CD4 cell counts (mean SE values: + 154 in the lopinavir/ritonavir arm versus 150 in nelfinavir arm).

Taking into account the time to loss of virologic response, 89 % of the patients in the lopinavir/ritonavir arm and 77 % in the nelfinavir arm were still responding at week 24 ($p< 0.001$).

With respect to AIDS defining events, the number of events appeared superior in the lopinavir/ritonavir (respectively: 30 events versus 19), however, it is unknown whether patients were symptomatic or not.

The applicant provided further data up to 48 weeks to confirm the sustained virological response with lopinavir/ritonavir. At 48 weeks, the proportion of patients with viral load below the limit of detection (< 400 copies/ml) accounted for 75 % in the combination arm versus 63 % in nelfinavir arm (ITT, M=F, $p<0.001$) with an acceptable rate of discontinuations (17 % versus 24 % respectively). The Kaplan-Meier estimates for the proportion of patients who were still responding at week 48 provided an additional demonstration of the superior antiviral activity of lopinavir/ritonavir (84 % [95 % CI: 80 %; 88 %] in lopinavir/ritonavir arm versus 66 % [95 % CI: 61 %; 72 %] in nelfinavir arm, Cox proportional hazards model, $p<0.001$). It was clarified that the amendment made to the protocol in relation to the dosage recommendation for nelfinavir (40 patients changed from TID to BID at 48 weeks), did not affect the overall results. The final report of this study was provided as part of the specific obligations to be fulfilled post-authorisation.

Subsequently, it was observed that at week +60, a statistically significant greater proportion of patients had sustained viral suppression in the lopinavir/rtv arm in comparison with the nelfinavir arm.

At week +60, the global percentage of treatment discontinuation was 25%.(22 % in lopinavir /rtv randomised group and 28 % in nelfinavir treated group.) Only six patients were reported to undergo change from their failing drug treatment to a salvage regimen. Another 31 subjects had reported NRTI substitution (12 lopinavir/ritonavir-treated and 19 nelfinavir-treated subjects) due to an adverse event primarily suspected as related to the study NRTI. This change was allowed by the protocol. However, even if all 31 subjects were considered virologic failures, the lopinavir/ritonavir-based regimen demonstrated superior antiviral activity compared to the nelfinavir-based regimen (71% versus 51; p<0.001%) at week +96, indicating reassurance in the treatment durability.**Study M98-888**

This randomised, open label, phase III study aimed to compare two antiretroviral strategies: lopinavir/ritonavir or a protease inhibitor chosen by the investigator in patients in failure with their current combination therapy including a protease inhibitor. In the reference arm, patients were mainly treated with dual protease inhibitors regimens. This study was ongoing and only 16 weeks data with preliminary 24 weeks data (on 50/118) were submitted. Total enrollment of 300 patients was planned.

Out of the 118 patients randomised (59 per arm) , 18 discontinued treatment (5 in the combination, lopinavir/ritonavir arm and 13 in the comparator).

At week 16, according to the ITT (Non Completer = Failure) population there was a difference in favour of the lopinavir/ritonavir group in terms of proportion of patients with undetectable viral load (73% (43/59) in the lopinavir/ritonavir group versus 54% (32/59) in the ISPI group). No difference between the two groups in this subset of patients could be demonstrated when considering on treatment population (80 % versus 76 %).

Clinical studies in special populations

Children (study M98-940)

Further to the evaluation of pharmacokinetic profile in the first phase of this study (between week 12 and 20), all patients were switched to 300/75-mg/m^2 doses.

The proportion of paediatric patients with HIV RNA levels < 400 copies/ml at week 12 by are presented by dose randomisation group in the following table:

Dose Group	**On-Treatment**	**ITT (LOCF)**	**ITT (NC=F)**	**ITT (M=F)**
Antiretroviral naive patients (without nevirapine)				
230 mg/57.5 mg	18/22 (81.8%)	18/22 (81.8%)	18/22 (81.8%)	18/22 (81.8%)
300 mg/75 mg	18/21 (85.7%)	18/22 (81.8%)	18/22 (81.8%)	18/22 (81.8%)
p-value comparing dose groups	>0.999	>0.999	>0.999	>0.999
Antiretroviral experienced patients (with nevirapine)				
230 mg/57.5 mg	17/26 (65.4%)	17/27 (63.0%)	17/27 (63.0%)	17/27 (63.0%)
300 mg/75 mg	21/28 (75.0%)	22/29 (75.9%)	22/29 (75.9%)	21/29 (72.4%)
p-value comparing dose groups	0.554	0.386	0.386	0.570

Results from the two doses groups were quite similar, although the small sample size did not all to draw definite conclusions. The efficacy and safety profiles of the oral solution appeared similar to

what was observed in adults. The proportion of patients with undetectable viral load (approximately 70 %) was comparable to the virological response obtained in adults. At 24 weeks, results have been presented according to the two dose groups, which is not pertinent since after the switch at week 12, all patients were treated with 300/75 mg/m^2.

Supportive studies

See dose-response studies, no further supportive studies have been submitted.

Clinical Safety

Patient exposure:

More than 2,000 adult and paediatric subjects were exposed to lopinavir/ritonavir during the clinical programme. These included 612 adults and 100 children naïve and protease inhibitor experienced patients and 561 healthy adults. Approximately 450 patients from the different phase I/II and III clinical studies were exposed to the dose intended for registration (400 mg/ 100 mg BID). In these pooled data (M97-720, M97-765, M98-957 and M98-863), the median duration of exposure was 196 days, the same as for the 100 paediatric patients in study M98-940. Median duration of exposure to lopinavir/ritonavir in study M98-888 was 125 days.

Adverse events and serious adverse event/deaths:

Across all 6 phase I/II and III studies in 712 adults and children, a total of 23 patients experienced adverse events resulting in premature study discontinuation (3 %). Of these, 13 were considered lopinavir/ritonavir related: digestive (8); elevated transaminases; rash (2: 1 with nevirapine); lactic acidosis; agitation insomnia (1: efavirenz).

Likewise 11 patients from these studies contracted serious adverse events considered related to lopinavir/ritonavir. These were heterogenous and included enterocolitis, diarrhoea, pulmonary oedema, cholecystitis, vasculitis, dizziness, deep vein thrombosis, , kidney stone fatty liver, encephalopathy and drug interaction. Generally these serious adverse events were not associated with discontinuation of therapy.

Of all the deaths reported (6), none were considered related to lopinavir/ritonavir. In the pooled data, most of the patients reported at least one adverse event (95 %). The most frequent were related to the digestive system (73 %). Overall the most frequently reported adverse vents were diarrhoea (52 %), nausea (25 %), headache (18 %), asthenia (17 %), pharyngitis (17 %), rash (16 %), pain (15 %) and infection (15 %). The overall incidence was similar between naïve and experienced patients.

Results from study M98-863 indicated that gastrointestinal tolerability seemed to be similar between lopinavir/ritonavir and nelfinavir treated patients. Digestive adverse events were the most frequent reported adverse event, occurred generally in the first 2 months of treatment and were the most frequent adverse event leading to discontinuation of the study drug. The median duration of diarrhoea was longer and the median time to onset for the first episode was shorter in the nelfinavir arm. The impact of diarrhoea on the quality of life should be further evaluated.

Cardiac adverse events

Considering the cardiac effects observed in dogs (prominent U waves associated with prolonged PR interval and bradycardia) during the toxicological study, a cardiac monitoring has been performed in phase I/II and III clinical studies to find detect any potential cardiotoxicity related to lopinavir/ritonavir. In common with observations in dogs, an augmentation of the PR interval was sometimes reported as well as a bradycardia (about 0.5 %). Two healthy volunteers in one phase I clinical study, had an increase of their QT interval (> 500 msec), but no apparent dose-response relationship could be shown. It was shown that baseline ECG parameters were not predictive of clinically ECG interval alterations on therapy. Some preclinical and clinical data were suggestive of a possible mechanism of potassium channel inhibition, however the clinical relevance was not apparent in the clinical studies. . Since lopinavir/ritonavir may increase blood levels of substances known to induce QT interval prolongation, which undergo a metabolism through CYP450 3A, appropriate warnings on their co-administration have been added in the Summary of Product Characteristics.

Pancreatitis

Cases of pancreatitis were reported in patients treated with lopinavir/ritonavir (3 in adult and one in paediatric patients) through the clinical studies up to 24 weeks. In the expanded access programme, 7 additional cases were reported. Given the multiple confounding factors, the causal relationship between pancreatitis and the fixed dose combination could not be established. Therefore monitoring is necessary as elevated triglycerides may play a contributing role in the development of pancreatitis. In addition, as pancreatitis is of particular concern in relation to the use of lopinavir/ritonavir, the applicant committed to further investigate this safety issue.

Laboratory findings

The most commonly laboratories findings reported were increases in GGT with values above 5 times the normal upper limit (9 %), total cholesterol with values > 3 g/l (9 %) and triglycerides with values above 7,5 g/l (8 %). Other very high chemistry values were glucose > 2,5 g/l (2 %), ASAT/ ALAT > 5N (2 %), and amylase > 2N (2 %). Higher percentages of these laboratory abnormalities occurred among antiretroviral-experienced than among antiretroviral naive patients.

A statistically significant decrease in total T4 and a trend to decrease for total T3 were observed among both naïve and experienced subjects whereas TSH levels were unchanged.

Lipids

Mean increases from baseline were consistently seen for total cholesterol and triglycerides in patients receiving the combination. Very high values of total cholesterol (>3 g/l) or triglycerides (>7,5 g/l) occurred in 12 % (64/538) and 11 % (60/538) respectively, of subjects receiving any dose of lopinavir/ritonavir with laboratory data available in M97-720, M97-765, M98-863, and M98-957 through 24 weeks of therapy. The median time of onset was about 56 days. In the pooled analysis, higher percentages of very high lipids abnormalities occurred among antiretroviral-experience subjects than among anti-retroviral naive subjects: cholesterol > 3 g/l: 21 % versus 6 % and triglycerides > 7,5 g/l: 23 % versus 5 %.

In M98-863, the rate of very high values of total cholesterol and triglycerides was higher in patients receiving lopinavir/ritonavir (7 % and 6% respectively) compared to patients receiving nelfinavir (3 % and 1 % respectively) through 24 weeks of therapy, although mean change from baseline in total cholesterol was similar (40 mg/dl versus 41 mg/dl respectively). In M98-863 and in M98-957, LDL/HDL ratios were not significantly changed from baseline at week 24. Pre-existing lipids elevations and lopinavir/ritonavir dose greater than 400-mg/100 mg were found to be associated with an increased risk of very high lipid elevations during lopinavir/ritonavir therapy. However the higher doses are only recommended in certain circumstances.

Lipid-lowering agents (statin and fibrate therapy) appeared to be effective in lowering cholesterol and triglycerides in these subjects. However, no detail was given on maximal values, for example patients with major hypertriglyceridemia (such as 20-30 g/l).

The applicant undertook to further monitor this safety issue, especially as very high levels of triglycerides have been observed up to more than 3000 mg/dl.

Liver functions

Very high ASAT and/or ALAT (> 5 ULN) values occurred in 4 % (20/538) patients receiving any dose of the combination in (M97-720, M97-765, M98-957 and M98-863 though 24 weeks of therapy. No case of symptomatic hepatitis attributed to lopinavir/ritonavir has been reported. Risk factors for very high ASAT or ALAT elevations include baseline ASAT and ALAT greater than the ULN, baseline hepatitis B/C infection and nevirapine use.

Safety in special populations

Children

Almost all the patients reported at least one adverse event. The pattern was generally similar to that of adults, except for common childhood diseases, eczema and taste perversion. The incidence of any adverse event of at least moderate severity and considered to be related to lopinavir/ritonavir was 6 %

compared to 35 % in adult patients. Rash (2 %) was the only such adverse event reported by two patients (one from each dose group). Liver enzymes and lipid elevations are similar to those observed in the adult populations. The experience in children below the age of 2 is too limited to draw definite conclusion on the safety of lopinavir/ritonavir in this age range.

Events of special interest

Lipodystrophy

A total of 23 cases of adverse events potentially representing fat redistribution ("lipodystrophy") syndromes were identified in adult's patients receiving lopinavir/ritonavir (approximately 4 %). As expected the incidence in antiretroviral experienced patients was higher than in naïve patients (~ 8 % versus 3 %). In study M98-863, lipodystrophy was identified in 2 % of patients receiving lopinavir/ritonavir treatment versus 1 % of patients receiving nelfinavir (7 versus 4 cases).

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.

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 Kaletra has been reworded in accordance with the CPMP recommendations to include, in section 5.2, data derived from patients. The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-

infected patients with normal hepatic function in a multiple dose study with lopinavir/ritonavir 400/100 mg twice daily (study M01-347). A limited increase in total lopinavir concentrations of approximately 30% has been observed which is not expected to be of clinical relevance.

Continuous assessment of Kaletra's long-term safety profile is performed throughout PSURs and the product information updated accordingly.

4. Overall Conclusion and benefit/risk assessment

Quality

The quality of lopinavir/ritonavir soft capsules and oral solution was considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. The two pharmaceutical forms are bioavailable under non-fasting conditions.

Preclinical pharmacology and toxicology

In vitro, lopinavir presents a potent intrinsic antiviral activity, with a resistance profile characterised by cross-resistance with indinavir and ritonavir but very low cross-resistance with saquinavir and nelfinavir. It was shown that at least 5 mutations are necessary to significantly reduce the phenotypic susceptibility to lopinavir.

The toxicological profile of the combination was assessed using a complete battery of toxicological studies. Identified target organs were liver (rats, mice and dogs), thyroid (rats only), gastrointestinal tract (dogs), heart (dogs), kidney (mice only) and haematological parameters (rats). Although the ratio of lopinavir/ritonavir was different from the one intended for clinical use, the results were considered relevant. A particular concern was raised regarding the cardiac effects observed in dogs (prominent U waves and prolonged QT intervals). The Purkinje fibers study was not considered adequate to exclude any cardiac effects associated with the use of lopinavir/ritonavir. Subsequent *in vitro* HERG studies, showed inhibition at the highest concentrations of lopinavir/ritonavir tested. The clinical relevance of these preclinical data is however unknown the combination did not alter the fertility parameters and was not teratogenic, but was slightly embryotoxicity in rats. Similar safety profiles were observed in adult and juvenile rats, which support a paediatric indication. Lopinavir was not mutagenic nor clastogenic. Carcinogenicity data did not raise concern in relation to the use of lopinavir/ritonavir in antiretroviral naive patients. .

Efficacy

The combination with ritonavir as a pharmacokinetic enhancer allows to achieve exposure to drug concentration highly above the level of viral inhibition of lopinavir (inhibitory quotient Cmin/C50 > 50).

The demonstration of the benefit of lopinavir/ritonavir containing regimen was mainly based on a well-designed main clinical study in antiretroviral naïve patients (M98-863). The percentage of patients with undetectable viral load reached 79 % at week 24 in the intent-to treat (non completer = failure) population compared to 71 % in the nelfinavir arm. 48 weeks data, presented in response to concern raised on the long-term efficacy of the combination, confirmed a sustained virological response with lopinavir/ritonavir.

Limited data in single protease inhibitor experienced patients suggested a significant virological response of lopinavir/ritonavir in this population since at 16 weeks 73 % of patients reached undetectable viral load (< 400 copies/ml, ITT analysis) (study M98-888).

In protease inhibitors multiple-experienced patients, lopinavir/ritonavir demonstrated a substantial virological suppression in patients harbouring viral strains with reduced sensitivity to other protease inhibitors. A significant reduction of viral load from baseline (- 1 log10 copies/ml) at week 2 was

demonstrated when lopinavir/ritonavir represents the unique change of a currently failing regimen including one protease inhibitor (study M97-765).

In children, similar efficacy was observed as that in adults but the number of children below the age of 2 years was too small to support an indication in age group.

The resistance profile of lopinavir seemed of interest with *in vitro* selected mutations somewhat different from those currently associated with ritonavir resistance. Analyses of cross resistance with PI suggests that decreased susceptibility to lopinavir correlated closely to ritonavir and indinavir, but did not corrolate closely with decreased susceptibility to amprenavir, saquinavir and nelfinavir. Resistance patterns associated with failure to lopinavir/ritonavir need to be further characterised. The same holds for the evaluation of salvage therapy of patients who have failed therapy with lopinavir/ritonavir.

Safety

The fixed combination lopinavir/ritonavir seems to be well tolerated and is in line with that of other available protease inhibitors. However the data were obtained from a limited number of patients exposed only short time. This was particularly true in children. Concerns were raised with respect to the long-term safety with regard to the high levels of triglycerides reported in patients treated with the combination and the occurrence of pancreatitis, particularly in antiretroviral naive patients. In addition considering that cardiac events were reported during preclinical and clinical studies, potential risks associated with lopinavir/ritonavir administration cannot be ruled out. In addition, as the oral solution contains a high amount of propylene glycol, appropriate warnings have been included to the Summary of Product Characteristics.

Benefit/Risk Assessment

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that the benefit risk ratio for Kaletra remains favourable in the treatment of HIV–1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents.

The Marketing Authorisation was initially granted under exceptional circumstances due to the lack of long-term data on efficacy and safety*. Following the evaluation of the data submitted post-authorisation, as part of the fulfilment of specific obligations, there are no grounds for maintaining the Marketing Authorisation under exceptional circumstances.

* Marketing Authorisation under exceptional circumstances refers to the fact that in exceptional circumstances an authorisation may be granted subject to certain specific obligations, to be reviewed annually.