SCIENTIFIC DISCUSSION

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

Norvir is presented as an oral solution (80 mg/ml) to be administered by means of a dosing device. Initially Norvir was also available as a hard capsule, however, due to the difficulties encountered in the manufacture of this formulation, the marketing authorisation for this pharmaceutical form has been later withdrawn, as indicated in the section 3 of Background information on the procedure. However a new formulation of ritonavir, Norvir 100 mg soft capsules has been further developed.

Active substance

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 and is much less soluble than Form I. However, during synthesis Form I is normally formed and used to prepare the finished product. The specifications and the routine tests are adequate to control the quality of the active substance. The impurities arising from synthesis and degradation have been well specified. Since the levels of the related impurities found in the batches used for the toxicological qualification are below the specified limits, some lower impurity limits have been set as requested.

Polyoxyl 35 castor oil is an important ingredient with regard to bioavailability and is suitably controlled prior to use.

Other ingredients

Excipients used in oral solution and soft capsules are in compliance with the European Pharmacopoeia, where relevant. For the other ingredients, the applicant provided adequate monographs.

Product development and finished medicinal product

The active substance ritonavir is characterised by low aqueous solubility, a lack of bioavailability when given in the solid state, instability once in solution under ambient conditions and a metallic taste. The development of the formulations intended for marketing and the choice of the excipients are adequate to deal with these characteristics. In the oral solution, an acceptable creamy caramel flavour is added to hide the metallic taste. The clinical development programme was based mainly on studies using the hard capsule formulation. The soft capsule formulation has been optimised with respect to the vehicle (co-solvent of ethanol, oleic acid and water) in order to accommodate the complete solubility in terms of 100 % Form II ritonavir and to allow storage at 5°C. As in the oral solution polyoxyl 35 castor oil has been added to improve the bioavailability.

Key steps of the manufacturing process and in-process control for the oral solution and the soft capsules are adequately described, including test designed to confirm the absence of undissolved ritonavir crystals due to the low solubility of polymorphic Form II of ritonavir. Results of batch analysis demonstrate the consistency of the manufacturing process for the two strengths.

For the oral solution and soft capsule, the proposed analytical procedures are adequate to control the quality of the finished product and are validated. The limits applied to the physical and chemical tests at the time of release and at the end of shelf life ensure that the product exhibits adequate quality throughout its life.

Stability

Results of stability tests of the oral solution are consistent to support the proposed shelf life. Degradation impurities specifications at the end of the shelf life have been tightened as requested.

Due to light sensitivity, the protecting amber polyethylene terephthalate bottle therefore offsets any potential degradation of the oral solution due to light exposure. In order to prevent a precipitation separation of the low-solubility polymorph II during storage, it is recommended that the oral solution is to be stored at a temperature of 20 – 25°C (in contrast to the soft capsule which may be stored at 5 °C) the unopened shelf life of the oral solution at this temperature is 6 months. In addition, appropriate warnings are given in the package leaflet and label, directing the patient to shake the bottle before use and to check for the presence of precipitate.

For the soft capsules, results from the stability studies support a shelf life of 12 months when stored at 5 °C. The formulation, which is different to the oral solution one, allows storage in a refrigerator without crystallisation until they are dispensed to the patient. Refrigeration by the patient is not required if used within 30 days and stored below 25°C.

Bioequivalence/bioavailability

Bioequivalence has been demonstrated between the original hard capsule formulation and the oral solution containing 80 mg/ml of ritonavir dissolved in a mixed system of water, ethanol, propylene glycol and polyoxyl 35 castor oil. Bioequivalence between the soft capsule and the oral solution has also been demonstrated.

The bioavailability of ritonavir in soft capsules and in soft capsules containing 12 % Form II crystals was not significantly different. In addition, when the soft capsule formulation has reduced ethanol level (12 mg/g) and contains up to 30 % of the nominal amount of ritonavir as Form II crystals, the bioavailability, of ritonavir is not significantly reduced compared to the oral solution. It was therefore demonstrated that the presence of crystals in the soft capsules, in the worst-case scenario has no clinical relevance.

2. Toxico-pharmacological aspects

Whereas nucleoside analogues inhibit reverse transcriptase, a viral enzyme acting at early stages of the HIV replication, ritonavir is a potent orally active peptidomimetic inhibitor of HIV-1 and HIV-2 aspartyl proteases.

The genome of HIV contains the retroviral genes gag and pol. These genes 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 to generate the respective structural proteins and enzymes. The enzyme responsible for this cleavage is HIV protease, it encoded by the pol gene and initially 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 in chronically infected, non-activated cells (i.e. following integration of proviral DNA into host cell DNA). Ritonavir 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 showed that Ritonavir has been demonstrated to be approximately 500 fold more specific for HIV protease (inhibition constant equivalent to 15 pM) than for any human aspartyl protease.

The *in vitro* antiviral activity of ritonavir was investigated against laboratory strains of HIV-1 and HIV-2 (tested in a variety of transformed and primary human cell lines) according to standard methods. The average concentration of ritonavir that inhibits 50 % and 90 % of viral replication *in*

vitro was found to be approximately equivalent to 0.02 µM and 0.11 µM respectively. The antiviral activity against HIV-1 was approximately 6-to-40-fold higher than against HIV-2 and equal potency was observed against pre-ZDV (zidovudine) sensitive and post-ZDV resistant HIV-1 in MT2 cells. Considering the high percentage of protein binding for ritonavir, EC50 value was found to increase more than tenfold in presence of plasma protein, which suggested that the antiviral activity *in vivo* might be attenuated by binding to plasma proteins.

Ritonavir's cytotoxicity was found to be minimal in relation to its antiviral properties. A therapeutic index superior than 1000 was established *in vitro*.

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 ritonavir and ZDV or didanosine (ddI). An additive effect on *in vitro* efficacy was observed when ritonavir was combined with either ZDV or ddI. This conclusion is only based on the results obtained with one laboratory HIV strain. The role of the biological phenotype (Syncytium-Inducing versus Non-Syncytium-Inducing phenotype) of HIV cultured from patients on monotherapy has not been defined.

In conclusion, the antiviral effect of ritonavir has been adequately demonstrated *in vitro*. Bibliographical references were, however, used to complete the assessment of ritonavir virology since the amount of virology data submitted was low.

Studies intended to investigate potential secondary pharmacological effects revealed limited effects of ritonavir on the central nervous system in mice and rats at doses between 5 and 50 mg/kg. Minimal effects were observed on the cardiovascular system of conscious rats and anaesthetised dogs. In the isolated guinea pig ileum, no antagonist or agonist effect of ritonavir was found. However the low exposure to ritonavir in these tests in comparison to human patients only allows a very low extent of extrapolation. No other tests were performed to investigate further pharmacodynamic actions of ritonavir.

Pharmacokinetics

The pharmacokinetic profile of ritonavir was determined in mouse, rat, dog and cynomolgus monkey using the well-characterised radiolabelled ritonavir and with a sufficiently sensitive and adequately validated HPLC preparative method. The bioavailability appeared to be dependent on species ranging form 71% in the male rat to 30 % in monkey, on gender in the case of rodents (the difference observed between male and female rats is unexplained), on the solvent used for the oral gavage dose, and to be dose-dependent. In all species, plasma protein binding is very high (98 % - 99.5 %).

Tissue distribution was investigated in female rats after a single oral dose of radiolabelled ritonavir equivalent to 50 mg/kg. Distribution into various tissues was time-dependent and except for the liver and the gastrointestinal tract for which levels were 12-15 fold those in plasma, tissue levels were

1-5 times as high as in plasma. Ritonavir may however be less active against viruses localised in the central nervous system (concentrations in the brain around 0.03-0.08 times total concentration in plasma). The potential passage of the placenta barrier and excretion in milk for ritonavir were not investigated.

After both iv. (5 mg/kg) and oral (20 mg/kg) administration in rats and dogs, it was shown that the main elimination pathway was via the bile and faeces and more than 92 % of the overall administered substance was recovered from faeces after 3-5 days. In the plasma, ritonavir was mostly found in its unchanged form. The renal elimination of ritonavir was negligible.

The metabolic profile of ritonavir from the bile of rat and dog and those from *in vitro* incubations with the respective microsomes showed no qualitative differences, as far as the major metabolites formed are concerned. Ritonavir is metabolised via various oxidative pathways, some of which are species-specific. According to the results of one study conducted in rats, ritonavir at doses 15-50 mg/kg/day during 14 days did not induce cytochrome P450 activity, but increased UDP-glucuronosyl transferase activity and liver microsomal protein content of the liver.

No formal results on pharmacokinetic interactions with other protease inhibitors were submitted.

The pharmacokinetic profile after repeated administration was established based on extensive toxicokinetic data obtained from the major toxicology studies. Ritonavir exposure was not linearly

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related to the dose. Deviations from dose-proportionality were observed in both rats (initially lower exposure followed by an increase in exposure) and dogs (increase in exposure after prolonged repeated dosing). It was suggested that these phenomena might be related to saturation of absorption or saturation of metabolism. In rodents, a gender difference in exposure was observed. A gender difference in enzyme activities responsible for ritonavir metabolism was suggested to explain this phenomenon.

The potential interconversion of ritonavir into other isomers *in vivo* was investigated neither preclinically nor clinically. Based on chromatographic analytical results, it was concluded that chiral inversion did not occur to any clinically relevant degree with ritonavir.

In general the preclinical pharmacokinetic profile was considered well defined. However, it should be remembered that exposure in toxicology studies was low when compared to the recommended therapeutic dose.

Toxicology

Single dose toxicity

The no observable effect level (NOEL) in mice was 320 and 200 mg/kg after oral administration in tests in with up to 2500 mg/kg p.o. Deaths occurred at 800 mg/kg.

NOEL in rats was 250 mg/kg p.o. and the approximate lethal dose by 2500 mg/kg p.o.

Repeated dose toxicity

Repeated dose oral toxicity was studied in mice (with doses up to 1000 mg/kg/day), rats and dogs with treatment duration up to 6 months in rats and dogs. AUC and C_{max} values were determined in all studies. The safety margin for ritonavir cannot be calculated because systemic exposure in different species, even at the highest dose was equal to or below human therapeutic exposure. In all three species the main target organs of toxicity were the liver and the eyes. The assumption that rodent liver and eye lesions (retina degeneration, retinal pigment epithelium hypertrophy) due to treatment were related to phospholipidosis (common phenomenon after administration of amphiphilic cationic compounds) was made even if several non-phospholipidosis associated lesions, in particular hepatocellular necrosis, pericholangitis and bile duct hyperplasia were observed in rodents.

The electron micrographs of both liver parenchyma and retina demonstrated mainly the presence of amorphous granula inclusion bodies, characteristic of phospholipidosis and this phenomenon appeared more predominant in the retina than in the liver.

Other lesions were reported throughout these studies such as the thyroid follicular epithelium hypertrophy in rats, gastrointestinal disorders in dogs, nephrotoxicity in rats with long-term treatment. Microgranulomas and histiocytosis occurred in several rat and dog tissues, especially in lymphoid organs as well as thymic atrophy. Moreover the potential immunotoxicity of ritonavir has not been adequately studied but there were no indications of such side effects in clinical studies. However, no further investigation in animals was requested in view of the clinical data.

Reproduction studies were conducted in both rats and rabbits. These studies did not reveal significant effects on fertility. In rabbits and rats, embryotoxicity occurred with maternally toxic high dose (75 mg/kg/day administered orally). In rat, cases of cryptorchidism were reported even with doses lower than the maternally toxic high dose (incidence equivalent to 4.23 % of foetuses in 13.04 % of the litters with 15 mg/kg/day). This finding, which may be regarded as a developmental retardation, did not lead to a contraindication of ritonavir in pregnant women. Peri/post natal toxicity study revealed no treatment-related effects.

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

Carcinogenicity studies performed in rodents are ongoing. Provision of the results is part of the obligations of the applicant to be fulfilled.

Environmental risk

Although no data are available, no toxicological risk for the environment is suspected.

The toxicity of the impurities and degradation products identified has been studied throughout acute toxicity studies in rats or mice in doses of up to 5000 mg/kg. Only one impurity showed a toxicological profile similar to ritonavir.

As the impurity and the degradation profile of the soft capsules differed from the original hard capsule formulation, toxicity studies were conducted. There was no evidence of a toxic and mutagenic potential of the degradants, and toxicology studies confirmed the safety of the revised specifications.

In experimental animals, ritonavir appeared to be fairly toxic particularly in rodents, even if the systemic exposure was low in the repeated dose toxicity studies. No safety margins were defined. A correction for the species-dependent differences in plasma protein binding may result in acceptable safety margins. The review of the interspecies comparison of exposure and the submission of C_{max} and AUC values after correction for protein binding, are therefore part of the specific obligations to be fulfilled.

3.   Clinical aspects

In vitro EC90 values for different HIV 1 and 2 strains were approximately 0.1 μM. However, in the presence of foetal calf and human serum these values increase considerably, up to approximately 3 μM. This is considered more relevant since ritonavir exhibits high protein binding in plasma. Until now, ritonavir has been shown to be one of the most potent antiretroviral drugs in terms of reduction of viral load. To confirm the effects of ritonavir observed during the preclinical development and to support the claimed indication, the submitted clinical dossier consisted of nine clinical trials. Two of them were pivotal phase III trials. In addition to these studies, results from a large number of studies on the pharmacokinetics, bioequivalence and interactions with other medicinal products are presented.

Further data were submitted on the pharmacokinetics, efficacy and safety in children to support the extension of the indication of Norvir to paediatric population.

Pharmacodynamics and pharmacokinetics

The pharmacokinetic profile of ritonavir was investigated in nearly all phase I and II trials of the development using different liquid formulations and an encapsulated liquid formulation. The semi-solid formulation, developed to attenuate the disagreeable taste is currently being used in ongoing clinical trials. All the formulations were bioequivalent. Because of the poor water solubility of ritonavir, no satisfactory intravenous form for human use is available. Some pharmacokinetic parameters have therefore not been defined (absolute bioavailability, volume of distribution, absolute clearance). Other parameters were determined by application of non-compartmental models. The analytical method used for the determination of ritonavir concentration in plasma is the same HPLC-UV assay as that used in animals.

Pharmacokinetics was studied in healthy adult volunteers and in HIV positive adults from both sexes. No apparent differences between populations were noticed and the diurnal variation of ritonavir pharmacokinetics observed in AUC, C_{max} and C_{min} is not expected to influence the efficacy/safety of ritonavir.

The pharmacokinetic characteristics of ritonavir are summarised in the following table.

Parameters	Units	Values (Mean ± SD)
C_{max} (600 mg single dose)	µg/ml	14.7 ± 3.3
C_{max} (SS [1], 600 mg q 12 h)	µg/ml	11.2 ± 3.6
T_{max} (600 mg single dose)	h	4.2 ± 0.9
C_{trough} (day 7, 600 mg q 12 h)	µg/ml	6.8 ± 5.1
C_{trough} (SS [2], 600 mg q 12 h)	µg/ml	3.7 ± 2.6
$V_{\beta/F}$ estimated (600 mg single dose)	l/kg	0.41 ± 0.25
t ½	h	3 – 5
CL/F (600 mg single dose)	l/h	4.6 ± 1.6
CL/F (SS [1], 600 mg q 12 h)	l/h	8.8 ± 3.2
CL_r	l/h	<0.1

[1] SS = Steady state, data from day 21

[2] SS = Steady state, mean of data from days 21 and 28

Ritonavir was highly bound to plasma proteins, mainly albumin and α1-glycoproteins (approximately 98 % - 99 %) and there was no sign of potential saturation. Limited data in patients confirmed that ritonavir is present in extremely low concentration in the cerebrospinal fluid, reflecting free concentration in the plasma.

The exploration of the metabolism using radioactive ritonavir revealed that the pathway was comparable with those observed in preclinical studies, as far as the major metabolites, formed via cytochrome P450 system (isozyme CYP3A4 and to a lesser extent CYP2D6), were concerned. From the four metabolites identified in humans, the isopropylthiazole oxidation metabolite, which is the only one found in systemic circulation, seemed to be as active as the parent compound.

The route of elimination is essentially hepatobiliary. After oral administration, 20 % to 40 % of unchanged ritonavir is recovered in human faeces. This observation is consistent with results obtained from preclinical studies. The pharmacokinetics of ritonavir is dose-dependent and more than proportional increases in the AUC and C_{max} were reported with increasing oral dose.

The influence of food on the pharmacokinetic parameters was investigated mostly during bioequivalence studies using different formulations. Ingestion of ritonavir after a meal was used in clinical trials. The influence of diluents used to hide the bad taste of the oral solution was also studied. Since no influence on pharmacokinetic parameters was observed with chocolate milk, a guidance to use this diluent was introduced in the Summary of Product Characteristics.

The pharmacokinetic profile of ritonavir was not evaluated in the following special populations: patients with impaired renal function, the elderly. Given the limited role of the kidney in the elimination of ritonavir, no significant effects are expected in patients with impaired renal function. In contrast since the liver, which is the main organ of elimination of ritonavir, hepatic impairment might affect the pharmacokinetics of ritonavir. To reflect this lack of information, appropriate information was included in the Summary of Product Characteristics.

New data on the pharmacokinetics of ritonavir in patients with mild and moderate hepatic impairment after single and multiple doses were provided. After single dose, pharmacokinetics in patients with mild to moderate hepatic disorders only slightly differed from that in patients with normal hepatic function. Steady state ritonavir levels were not statistically significantly different in subjects with mild impairment compared to normal patients, without dose normalisation. There are currently too limited data to confirm that ritonavir pharmacokinetics is not substantially affected by mild to moderate hepatic impairment, as reflected in the relevant section of the Summary of Product Characteristics. In severe hepatic impaired patients, the use of ritonavir is contra-indicated.

Subgroup analyses revealed a statistically significant reduction in AUC (about 18 %) in smokers versus non-smokers. This phenomenon for which the mechanism involved has not been elucidated, is considered to be slightly clinically relevant. Another subgroup analysis of patients with high body weight versus low body weight revealed that AUC values did not correlate with body weight. It was

also reported that there was no relation between CYP2D6 genotype, known as "poor metaboliser" and ritonavir clearance.

In children, the pharmacokinetics has been determined on the basis of data obtained in 49 children aged more than 2 years old from two studies, studies M95-310 and ACTG 338:

In study M95-310, where patients were assigned in a non-randomised way to one of the four doses treatment groups, and received ritonavir monotherapy at doses ranging from 250 to 400 mg/m^2 BID for 12 weeks. After 12 weeks patients could receive ritonavir in combination with zidovudine (90 mg/m^2 QID) and/or didanosine (90 mg/m^2 BID). Results obtained from an interim analysis were presented. Since at the cut-off time only 4 patients were less than 2 years old, it was decided to exclude them from the analysis and, as a consequence, to exclude this age group from the claimed indication. A total of 37 HIV-infected children entered therefore in the analysis.

In study ACTG 338, of a total of 298 patients who entered in the study, 162 were included in the interim analysis of the viral response at 12 weeks and 24 were included in the pharmacokinetics analysis. Patients were antiretroviral experienced but protease inhibitors naive. Patients were assigned to one of the following treatment regimens:

Treatment A: zidovudine (160 mg/m^2 TID) in combination with lamivudine (4 mg/kg BID)

Treatment B: ritonavir (350 mg/m^2 BID) in combination with zidovudine (160 mg/m^2 TID) and lamivudine (4 mg/kg BID)

Treatment C: ritonavir (350 mg/m^2 BID) in combination with stavudine (1 mg/kg BID)

Results obtained from both studies are summarised in the table below:

Dose (mg/m^2) BID	N	Age (years)	Body weight (kg)	Cmax SS ($\mu g/ml$)	Ctrough SS ($\mu g/ml$)	Cl/F (L/h/ m^2)	AUC $_{0-12h}$ ($\mu g.h/ml$)
STUDY M95-310							
250	7	8.2 ± 3.6	21.3 ± 6.0	9.7 ± 4.9	3.3 ± 3.4	6.0 ± 3.9	58.3 ± 32.7
300	9	8.8 ± 4.5	26.9 ± 10.3	10.9 ± 3.7	2.2 ± 1.4	5.7 ± 2.7	62.9 ± 26.6
350	11	9.0 ± 3.9	30.4 ± 22.1	11.4 ± 4.2	2.1 ± 1.9	7.4 ± 4.0	59.5 ± 26.7
400	10	6.2 ± 4.0	20.1 ± 11.5	15.9 ± 9.9	5.5 ± 4.0	6.4 ± 5.2	100.0 ± 63.6
ACTG 338							
350 B + C	12		24.6 ± 10.9	13.3 ± 8.8	2.9 ± 3.4	5.8 ± 3	76.6 ± 56.3
B[B]	6		27.8 ± 14.8	9.2 ± 5.1	1.7 ± 1.2		54.0 ± 35.1
C[C]	6		21.5 ± 3.4	18.1 ± 10.1	4.3 ± 4.8		102.9 ± 67.7
ADULTS							
600 mg BID				11.2 ± 3.6	3.7 ± 2.6	4.8 ± 1.8	

B: 350 mg/m^2 BID ritonavir in combination with ZDV 160 mg/m^2 TID and lamivudine 4 mg/kg BID.
C: 350 mg/m^2 BID ritonavir in combination with stavudine 1 mg/kg BID alone

With respect to M95-310 study, at steady state (day 28), the plasma concentrations after ritonavir monotherapy administered at the doses 300 to 350 mg/m^2 were similar to those observed in adults but the trough levels were lower. On the other hand, the higher dose level (400 mg/m^2 BID) showed a higher steady state C_{max} and C_{trough} values than in adults. Although the submitted data are limited, no statistically effect of gender, age and body weight on the pharmacokinetics parameters was observed.

In ACTG 338, the dose 350 mg/m^2 BID was chosen based on the former study. Plasma concentration was lower in the group receiving ritonavir in combination with zidovudine and lamivudine than the group receiving the combination with stavudine alone. Since no explanation can derive from adult data, the small groups and intersubject variability could have been the reasons. This issue will be further investigated based on data obtained from population pharmacokinetics.

Results did not suggest any pharmacokinetic interactions between ritonavir and stavudine and lamivudine, but the potential interactions will be further investigated. As already observed in adults, ritonavir decreased the plasma concentrations of zidovudine, however the level of the decrease appeared higher in paediatric than in adults. It was considered acceptable that at the present time no warning is needed in the Summary of Product Characteristics with respect to decreased plasma concentration of ZDV when co-administered with ritonavir.

Considering the above-mentioned pathway for ritonavir metabolism**,** the potential **pharmacokinetic interactions** of ritonavir with either drugs, which are substrates of the cytochrome P450 family, or drugs frequently co-administered with antiretroviral drugs, were investigated. The main findings were as follows:

Medicinal products used in the same indication

Zidovudine co-treatment (200 mg every 8 hours) did not influence ritonavir pharmacokinetics, when administered at 300 mg every 6 hours after a meal whereas ritonavir reduced ZDV C_{max} and AUC_{0-24h}, by an average of 27 % and 25 %, respectively. However, no influence on ZDV glucuronide exposure and consequently on the ZDV metabolite AMT was noted. This conclusion has been extrapolated to the 600 mg twice daily dose regimen based on the fact that the same total daily dose (1200 mg) was used in the study.

A similar effect on ddI C_{max} (-16 %) and AUC_{0-24h} (-13 %), at a ddI dose equivalent to 200 mg every 12 h in the fasted state was observed. This reduction in ddI exposure by ritonavir, although statistically significant, was considered not to require any dose adjustments.

The pharmacokinetic interaction between saquinavir and ritonavir was demonstrated in two trials carried out in healthy volunteers, consisting of one single (M95-409) and one multiple dose (M95-248) study. Results from both studies showed that the pharmacokinetics of ritonavir were not influenced by concomitant administration of saquinavir whereas the pharmacokinetics of saquinavir were markedly affected by ritonavir as shown in the single dose study (AUC increase > 50 fold and C_{max} increase > 22 fold) and multiple dose study (AUC increase 18-35 fold). In an open-label (M96-462), multi-dose, randomised, multicentre trial, the safety and efficacy of 4 different combination regimens of ritonavir and saquinavir was investigated. This study involved 141 protease inhibitors naive patients of both sexes who had CD4 cell counts ranging from 100-500 cells/µl and baseline HIV RNA levels of ≥ 5,000 copies/ml. Virologic response, defined as the percentage of patients with viral load under undetectable effect (< 200 copies/ml), was obtained in the majority of patients between 8-24 weeks (range 60-90 % depending on the dosing regimen). The highest response was found with the dosing regimen 400 mg ritonavir + 400 mg saquinavir bid. Due to safety reason, this combination regimen may be considered as the best regimen for further exploration of benefits of combinations with other anti-retroviral combination regimens such as nucleoside reverse transcriptase inhibitors.

Interaction data with other protease inhibitors became available during the post-marketing phase.

In healthy subjects, 200 to 400 mg of ritonavir twice daily given with a single 400 to 600 mg indinavir dose increased the indinavir AUC by 185 to 475%, C_{max} 21 to 110%, and C_{8h} 11 to 33-fold, relative to 400 to 600 mg indinavir given alone. Concomitant administration of 400 mg ritonavir and 400 mg indinavir twice daily with a meal yielded a similar indinavir AUC, a 4-fold increase in Cmin and a 50 to 60% decrease in Cmax as compared to those resulting from administration of indinavir 800 mg three times daily under fasting conditions.
The efficacy and safety data of ritonavir in combination with indinavir are limited. However, published data on an open uncontrolled study suggested that treatment with 400 mg BID ritonavir/ 400 mg indinavir in a combination with double nucleoside regimen did not appear to induce kidney stones.

Pharmacokinetic data showed that concurrent ritonavir 400mg bid significantly increases the concentrations of M8 (the major active metabolite of nelfinavir), and results in a smaller increase in nelfinavir concentrations. In a study in 10 patients nelfinavir 750mg and ritonavir 400mg twice daily yielded slightly higher nelfinavir AUC (160%), C_{max} (121%) and C_{trough} (123%) than historical data for nelfinavir 750mg tid monotherapy. The AUC of M8 was increased by 347%.

Wide clinical experience with ritonavir used as pharmacokinetic enhancer (at low doses of 100-200 mg once or twice daily) to boost the plasma concentrations of other protease inhibitors in HIV-infected adult patients has become available. For Fortovase and Invirase, doses at 1000 mg twice daily in combination with ritonavir 100mg bid, resulted in systemic exposure over 24 hours greater than those achieved with Fortovase 1200 mg three times daily. Likewise, for amprenavir, when given in combination with ritonavir, reduced doses of both medicinal products (amprenavir 600 mg twice daily and ritonavir 100mg twice daily) should be used, since booster doses of ritonavir given together with amprenavir result in clinically significant increases in amprenavir AUC and C_{min} with variable effects on maximum concentration.

Data showed that in healthy volunteers receiving 500 mg ritonavir twice daily with efavirenz 600 mg once daily, the steady state AUC of efavirenz was increased by 21 % and an associated increase in the AUC of ritonavir of 17 % was observed. This dose regimen led to a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes).

Other medicinal products

Pharmacokinetic interactions with fluconazole and cotrimoxazole were not considered clinically relevant.
The influence of ritonavir on the pharmacokinetics of rifabutin and its metabolite, characterised by a multifold increase of the exposure probably due to an inhibition of hepatic metabolism, was considered clinically relevant. Therefore, the concomitant use of ritonavir and rifabutin is contraindicated.

Clarithromycin exposure was markedly increased with concomitant ritonavir treatment due to an inhibition of its active metabolite formation. This finding is considered to be without clinical relevance since the inhibition is counterbalanced by an increase of AUC of parent drug. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function.

Dosage reduction of desipramine should be considered in patients taking the combination.

The influence of ritonavir on ethinyl estradiol exposure is marked by an important decrease, probably due to an enzymatic induction, therefore an increased dose of oral contraceptives containing ethinyl estradiol or alternate methods of contraception should be considered. A similar observation was noted with theophylline after a period of time. Ritonavir, added to theophylline at steady state (at day 5 of theophylline administration), reduced C_{max}, C_{min} and AUC_{0-24h} of theophylline after 10 days by an average 32 %, 57 % and 43 % respectively. In concomitant use with ritonavir, an increased dosage of theophylline may be required.

In summary, potential interactions with ritonavir were explored throughout formal interaction trials, interaction analysis of the larger clinical trials and theoretical considerations even if in most of the studies the ritonavir dose administered was lower than the recommended dose. To reflect the results of the influence of ritonavir on these medicinal products adequate descriptions and cautions have been introduced to the Summary of Product Characteristics. It was suggested, however, that potential interactions based on displacement from protein binding should have been investigated. In addition, as ritonavir was shown to be an *in vitro* potent inhibitor of CYP3A and CYP2D6, many potential interactions are expected as stated in the Summary of Product Characteristics.

A number of new interactions were highlighted following the submission of case reports during the post-marketing phase. These new interactions related to cases of ergotism associated with the combination of ritonavir with ergotamin containing medicinal products. Several cases of already known or suspected interactions with disopyramide, mexiletine, nefazodone and fluoxetine, all metabolised by CYP 450 isoenzymes were described. These reports suggested cardiac and neurological events as a result of the combination of ritonavir with these drugs. An update on the safety sections of the Summary of Product Characteristics was therefore recommended.

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Results from new interaction studies were provided. Ritonavir metabolism was not significantly influenced by co-administration of ketoconazole at the dose of 200 mg once daily. On the other hand, ritonavir at the dose of 500 mg bid inhibited the metabolism of ketoconazole, which led to an increase of mean Cmax of ketoconazole by 1.5 fold and of mean AUC $_{0-24}$ by 3.4 fold. This could have gastrointestinal and hepatic consequences. Ritonavir administered at 500 mg bid to steady state levels, decreased AUC and C_{max} of methadone by about 40 % and mean clearance was statistically significantly increased from 7.8 to 12.0 l/h. These potential interactions have been adequately reflected in the Summary of Product Characteristics.

Considering the suspected fatal interaction between ritonavir and amphetamines or amphetamines-like substances, the CPMP recommended the inclusion of this interaction into 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*), 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.

During the post-marketing phase, case reports showed that warfarin concentrations might be affected when co-administrated with ritonavir and therefore the monitoring of anticoagulation parameters is now recommended as mentioned in the SPC. This interaction has been further evaluated.

Bioequivalence

During the clinical programme of ritonavir, different development formulations, either oral solution or semi-solid presentations were administered. Therefore six bioequivalence trials to allow bridging of the clinical trial results were carried out. All the available formulations were bioequivalent to the reference, which is an encapsulated solution containing 100 mg ritonavir. Since the original submission, the bioequivalence study comparing the relative bioavailability of the semi-solid oral capsule with the oral solution confirmed that these marketed formulations are also bioequivalent.

A new pharmaceutical form of Norvir, soft capsules containing 100 mg ritonavir, developed to overcome dissolution problems seen with hard capsules, received Marketing Authorisation in 1999. The clinical development focused on the demonstration of the bioequivalence between the new formulation and the hard capsules (later withdrawn from the market) and oral solution formulations. Four bioequivalence studies have been performed. The soft capsules were bioequivalent to the marketed oral solution formulation. Although mean AUC values under non-fasting conditions were higher that under fasting conditions, the intake of food did not statistically significant affect the absorption of ritonavir from the soft capsule.
With respect to safety, the bioequivalence studies did not reveal any new adverse events. Both new and already authorised formulations seem to be equally well tolerated on the basis of four bioequivalence studies in healthy volunteers.

 Therapeutic efficacy

Nine therapeutic clinical trials in HIV patients were performed including two major phase III studies, involving a total of 1684 patients. The antiretroviral effects of ritonavir and their consequences on the immune system were evaluated in all nine therapeutic trials on the basis of biological markers such as the amount of plasma HIV RNA and CD4 cell counts. In addition, both major Phase III trials are investigating clinical efficacy in terms of clinical endpoints such as disease progression and mortality rate. However, at the time of the original opinion, clinical endpoints data were only available in advanced patients (M94-247) results.

In vitro the IC90 for viral replication in human-serum containing assays was approximately 2μg/ml. This value was selected as the desired lower limit of concentration (C_{trough}) to be achieved in the dose-ranging studies. In phase II studies total daily doses ranging from 600 to 1400 mg were tested for their

effects on the biological markers, CD4 cell counts and plasma HIV RNA usually determined by the branched chain DNA technique.

Four phase II studies with ritonavir monotherapy were conducted. However, one of these studies was judged to be too small (6 patients) to give relevant information. One open-label multicentre study (M94-229) assessed two orally administered dosing regimens. The remaining two studies (M93-112, M93-134 and their respective open extension phase) have a similar design, double blind, placebo controlled, randomised, parallel groups. Female and male HIV positive patients with CD4 cell counts > 50 cells/mm^3 received doses of ritonavir encapsulated liquid ranging from 600 mg to 1200 mg/day in bid, tid or qid fashion for 28 days. The overall results of M93-112 showed that no dose effect on viral load and on CD4 count was observed during the first 28 days of treatment. In contrast, during the open label extension phase after 28 days of treatment, the 500 and 600 mg bid doses led to a higher suppression of viral load and increase in CD4 count compared to the lower dose up to week 20. The effect with 500 mg bid appeared, however, to deteriorate and approached the baseline value in a similar way as the lower dose levels. These results must be treated with caution due to the design of these trials (open label follow-up, small number of patients) and the sensitivity of the assay used for the determination of the viral load (lower limit of quantification equivalent to 10,000 viral copies per ml i.e. 4 log 10 viral copies/ml. By comparison the lower limit of quantification with the HIV RNA PCR technique is 200 viral copies per ml i.e. 2.3 log 10 viral copies/ml). With respect to results obtained from the other studies, within the first week of treatment, virologic and immunologic changes in ritonavir groups were observed. At day 7, patients in all ritonavir arms had approximately -0.7 $\log_{10}$ reduced viral load in comparison with baseline. Over the 28 days period, no dose-response relation with respect to both biological markers was observed.

From these studies, based on the results on virology, immunology and safety, ritonavir 600 mg bid was selected for further investigation.

Based on the results from studies M95-310 and ACTG 338, the recommended dose of 350 mg/m^2 twice daily was considered acceptable for the safe and efficient use in children.

One open label phase II trial (M94-208) in adult's combination therapy was carried out in France. This small multicentre, uncontrolled, open, phase II study aimed to investigate the efficacy of combination therapy (ritonavir-ZDV and ddC). The efficacy was evaluated based on changes in viral load, as measured by HIV RNA PCR technique, and in CD4 cell counts. Naive patients (32) with CD4 cells count ranging from 50 to 250 cells/µl received 600 mg q12h of ritonavir and at day 15 200 mg q8h of ZDV and 0.75 mg q8h ddC were added. Although the results of this study should be interpreted with caution due to the design of the study, the effects of the combination therapy on plasma viral load were important. The maximum mean decrease was 1.92 $\log_{10}$ particles at week 8 and the mean decrease at week 20 was 1.76 $\log_{10}$ particle/ml.

Throughout all phase II studies, thyroid function was routinely monitored and some changes were observed. While mean TSH remained well within the normal limits, there was a statistically significant decrease of T4 (thyroxin) levels and a trend towards increased T3 levels. The precise mechanism for these changes is not elucidated and a statistical correlation of changes in thyroid parameters and the occurrence of asthenia is currently under investigation. Up to now based on observations from clinical studies it is considered that these changes are without clinical relevance.

The first main study (study M94-247) was designed to compare ritonavir 600 mg BID versus placebo, in addition to whatever concurrent antiretroviral therapy in patients with advanced HIV infection (CD4 ≤ 100 cells/µl) who had previously received reverse transcriptase inhibitor therapy. One particular feature of this study which involved 1090 adults is that these patients have been extensively pre-treated for at least 9 months with no change during the last 6 weeks.

Double-blind treatment duration of at least 16 weeks was followed by an open label ritonavir therapy. The primary endpoint is clinical progression of HIV disease defined as death, a new AIDS defining illness or selected disease recurrence. Other endpoints include viral load as measured by PCR method and CD4 cell count. The first planned analysis of the protocol **(interim I)** was conducted after a subgroup of 150 patients with more than 15,000 HIV RNA particles had completed the 16 week double blind treatment period.

At the date of **interim I report**, no analysis of the primary clinical endpoint was available but results on the biological markers were analysed.

Average changes from baseline in viral RNA level and CD4 cell counts over 16 weeks are presented in table Table 1

	Treatment group	N	Mean baseline	Mean change	SE
Viral RNA level (log$_{10}$ copies/ml)	Ritonavir	80	5.29	-0.79	0.066
	Placebo	79	5.24	-0.01	0.066
CD4 cell counts (cell/µl)	Ritonavir	108	31.0	33.2	3.00
	Placebo	103	26.4	-0.8	3.07

The differences of the means over 16 weeks between placebo and ritonavir for both viral load and CD4 cell count were statistically significant. Analyses of changes from baseline in viral RNA levels showed that the effect of ritonavir was reduced over time. However, this decline in the effect on viral load did not seem to be paralleled by a decrease of CD4 cell counts. It is possible that CD4 cell counts could follow the pattern of HIV RNA plasma levels with a certain lagtime, although this should be confirmed through a longer follow-up.

With regard to **virological response**, defined as two consecutive decreases from baseline of at least 90% (1 log$_{10}$) in HIV viral RNA (the duration of this response was analysed by Kaplan-Meier methodology), 45% of patients from the ritonavir group showed virological response during the first 16 weeks compared to none in the placebo group. The percentage of patients who responded during at least 8 weeks was 35% (24% for 12 weeks) and the onset of response was in most cases by week 2.

With regard to **immunological response**, defined as two consecutive measurements indicating an increase from baseline of at least 50 cells (the duration of this response was analysed by Kaplan-Meier methodology), 29 % of patients from the ritonavir group showed a CD4 lymphocyte response during the first 16 weeks compared to 2 % in the placebo group. The percentage of patients who responded during at least 8 weeks was 26 % (25 % for week 12) and the onset of the response was in most of cases by weeks 2-4.

Given that of the virological responders in the ritonavir treatment group, 58 % also showed immunological response a strong relationship between the virological and immunological responses was established.

Subgroup efficacy analyses for the following groups, baseline HIV RNA level or CD4 cell counts, prior antiretroviral therapy and gender also revealed consistent results.

Other clinical endpoints

The difference of the means for increases in CD8 cell count over 16 weeks between placebo and ritonavir was statistically significant.

No difference was found with respect to weight, Karnofsky performance score and 3 different quality of life questionnaires.

The second planned analysis of the protocol (**interim II report**) was conducted after a subgroup of 191 patients has experienced documented AIDS-defining events (CDC class C) or death beyond the first 28 days after randomisation.

Mortality rate

At the cut-off date of the interim report, 26 deaths occurred in the ritonavir group (543 patients) compared to 46 in the placebo group (547 patients). In the intent to treat analysis (including all randomised patients), the difference in favour of ritonavir is therefore statistically significant.

Death or disease progression

The number of patients who experienced disease progression or death events was 86 in the ritonavir arm and 181 in the placebo arm respectively. A statistically significant difference in favour of

ritonavir was demonstrated which represents a reduction of 56 % in the risk of death or disease progression (p < 0.001). An analysis of patients with first event occurring at least more than 28 days after start of treatment also confirmed a reduction of disease progression with ritonavir. The rate of follow-up loss was 11,9 % in the placebo group and 17,5 % in the ritonavir group respectively. However, the updated analyses of survival and time to disease progression or death submitted by the applicant confirmed the favourable impact of Norvir therapy. The provided subgroup analysis according to treatment regimens suggests (e.g. of subgroups of > 60 patients per arm) that patients on combination therapy have a lower risk of disease progression than patients on ritonavir monotherapy (20 – 25 % of the present patient sample). The latter is also consistent with the effects of these treatments on the viral load.

With regard to this study, several points should be considered. An attempt to establish a relationship between changes in HIV RNA level and CD4 cell counts and the disease progression in a patient subgroup was made. Additional information submitted demonstrated that large average decreases in HIV RNA levels and increases in CD4 cell counts were associated with reduced risk of disease progression. A demonstration of superiority of viral load as a surrogate marker over CD4 cell counts in predicting the clinical outcome of ritonavir was also submitted but results were interpreted with caution. The limited follow-up period of 6 months does not allow predicting the clinical benefit of the combined therapy for longer periods. The most frequently used nucleoside analogues in this study were zidovudine, stavudine, didanosine and zalcitabine. The most optimal combination of ritonavir with an antiretroviral nucleoside analogue is unknown. It was therefore considered necessary to conduct further optimisation studies on combination therapies with ritonavir and other approved antiretroviral agents in patients with advanced HIV disease.

The final study report provided described the results of the double-blind phase of the study during which the median duration of exposure to ritonavir was 182 days and median duration of follow-up was 217 days. At the end of the double-blind phase of the study, 114 (21.0 %) patients randomised to receive ritonavir and 205 (37.5 %) patients randomised to receive placebo had experienced disease progression or death. A statistically significant difference in favour of the ritonavir group was demonstrated which represents a reduction of 49 % in the risk of disease progression or death (p < 0.001). With respect to the survival analysis, at the end of the double-blind phase of the study, 38 (7.0 %) patients randomised to receive ritonavir and 63 (11.5 %) patients randomised to receive placebo had died. The median duration of follow-up was 202 days for patients in either randomisation group. A statistically significant difference in favour of the ritonavir group was demonstrated which represents a reduction of 40.4% in mortality (p = 0.012). In a "worst case scenario" (e.g. patients lost to follow-up, dropouts) the reduction in the risk of disease progression or death was still statistically significant (45 %) meanwhile the reduction in mortality of 26.3 % was not statistically significant. With respect to changes in biological markers measured in a subset of patients, the average changes from baseline reported were similar to the one provided in the original submission. Mean decreases over time showed attenuation of the effect of ritonavir. The quality of the long-term efficacy results for the period beyond the first 16 weeks of double-blind treatment was compromised due to the liberal use of concurrent antiretrovial therapies. However, the global beneficial clinical results of ritonavir during the first phase of the pivotal clinical study in these advanced HIV-infected patients were sustained and confirmed.

The second main study (study M94-245) was designed to compare the antiviral and immunologic effects of ritonavir 600 mg BID monotherapy versus zidovudine 200 mg tid monotherapy versus the combination of these two drugs in patients who have never received prior antiretroviral treatment and who have CD4 cell counts more than 200 cells/µl (but < 500 cells/µl for the overwhelming majority of patients). This study is a 1 year double-blind study including an open label extension phase with ritonavir monotherapy. An interim analysis was performed after a 16 weeks treatment period. The primary endpoints were changes in plasma HIV RNA as measured by HIV RNA PCR technique and CD4 cell counts.

The table below presents the average changes from baseline in viral RNA level and CD4 cell count over 16 weeks.

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	Treatment group	N	Mean Baseline	Mean change	SE
Viral RNA level ($\log_{10}$ copies/ml)	Ritonavir-ZDV	116	4.92	- 0.80 [1]	0.068
	Ritonavir	118	4.91	- 1.03 [2,3]	0.068
	ZDV	121	4.88	- 0.42	0.066
CD4 count (cell/µl)	Ritonavir-ZDV	117	360.1	34.9 [4]	7.28
	Ritonavir	118	365.3	62.0 [2,3]	7.19
	ZDV	120	366.2	10.7	7.02

[1] Statistically significantly superior to ZDV ($p < 0.001$); [2] Statistically significantly superior to ZDV ($p \leq 0.05$); [3] Statistically significantly superior to ritonavir-ZDV ($p \leq 0.05$); [4] Statistically significantly superior to ZDV ($p = 0.018$)

The overall results showed that all three treatments produced statistical significant decrease in viral load and increase in CD4 cell count, but ritonavir treatments were significantly better than ZDV monotherapy. However, unexpectedly, given the synergistic effect observed *in vitro*, ritonavir monotherapy was better than ritonavir-ZDV combination therapy. These paradoxical results were not clarified, although decreased compliance caused by increased toxicity of the combination therapy might have contributed to the lower performance of the combination treatment.

Virological response, as previously defined, was demonstrated in 64 % of patients in the ritonavir arm against 49 % in the combination therapy arm. Only 7 % of patients in the ZDV group showed a virological response. In the ritonavir group, 51 % of these patients responded during at least 8 weeks. The maximum reduction of viral load occurred in all arms at about week 2 and did not fully remain at this level during the 16 weeks treatment period.

With regard to the evaluation of the **immunological activity**, the percentages of patients who demonstrated a CD4 lymphocyte response were 59 % and 48 % in the combination therapy and the ritonavir arm respectively. In the ritonavir group, 55 % of these patients responded during at least 8 weeks. In contrast, the maximum increase of CD4 cell count occurred in all arms at about weeks 2-4 and maintained at this level during the 16 weeks treatment period.

A strong relationship between virological and immunological responses has been established in the ritonavir group.

A subgroup analysis, according to baseline HIV RNA level and CD4 cell count seemed to confirm the previous results. It was interesting to note that in patients with less than 350 CD4 cell/mm^3 the combined therapy ritonavir-ZDV enhanced CD4 cell count slightly better than ritonavir monotherapy. However this effect decreased with increasing baseline CD4 cell count.

With regard to other clinical endpoints, ritonavir either monotherapy or in combination showed significantly favourable effects on CD8 cells count. In contrast only in the ZDV monotherapy treatment group was an increase in body weight observed.

The final study report provided described the results of the double-blind phase of the study. While the duration of the double-blind period varied, all patients completed at least 48 weeks of treatment. A total of 123 patients prematurely discontinued double-blind treatment, 42/118 (36 %) in the ritonavir arm, 27/121 (23 %) in the ZDV arm and 54/117 (47 %) in the combination arm, mostly due to adverse events. The average changes from baseline in viral load were − 0.88 $\log_{10}$ in ritonavir versus − 0.66 $\log_{10}$ in ritonavir/zidovudine group versus − 0.42 $\log_{10}$ in zidovudine group. A significantly larger proportion in the ritonavir group (65 %) than in the ritonavir/ZDV combination group (43 %) or the ZDV group (13 %) displayed a virological response, as previously defined. Statistically significantly larger proportions of patients in the ritonavir group (64 %) and combination therapy (57 %) groups than in the ZDV group (44 %) experienced two consecutive measurements showing an increase from baseline of at least 50 cells/ml. The obtained effect was therefore modest and unexpectedly the combination ritonavir/ZDV appeared less effective than ritonavir alone. Nonetheless,

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the number of patients exposed to controlled exposure to ritonavir alone or in combination with ZDV were significantly reduced throughout 48 weeks period making the value of prolonged experience with ritonavir regimens in this very small patient population non conclusive. In overall, results did not allow any conclusion on the clinical benefit of combination therapy with ritonavir and ZDV in less advanced HIV-infected patients with no prior antiretroviral therapy. The results obtained from the study M94-247, which revealed a clinical benefit of ritonavir in patients with advanced HIV disease, cannot be extrapolated to patients with less advanced HIV. Therefore to support the claimed indication further evidence of the beneficial clinical effect of ritonavir in the recommended dosage as in HIV-infected patients with less advanced HIV disease is requested.

On the basis of the limited data on monotherapy and because of concern about the emergence of resistance, the use of monotherapy cannot be recommended.

Studies in children

The efficacy of ritonavir in children has been demonstrated based on data obtained mainly from ACTG 338 up to 48 weeks. The primary endpoint is the proportion of children reaching an undetectable level of plasma HIV RNA as measured by the Nucli Sens Assay with a lower detection limit of 400 copies/ml and the secondary endpoint defined is virologic failure.

The baseline characteristics were the following: median age of 7.1 years, median HIV RNA levels of

4.34-log10 copies/ml and a median CD4 of 671 cells/mm^3.

In an intent-to-treat analysis, the proportion of patients with undetectable HIV RNA level who had detectable RNA at baseline displayed in the following table:

	Treatment A	Treatment B	Treatment C
Baseline median log$_{10}$ copies/ml (N)	4.40 (100)	4.26 (97)	4.41 (99)
Proportion with undetectable HIV-RNA (< 400 copies/ml) at Week 4	25% (24/95)	50% (46/92)	54% (50/93)
Proportion with undetectable HIV-RNA at Week 12	12 % (11/95)	55% (51/92)	56% (52/93)
Proportion with undetectable HIV-RNA at Week 24	8 % (8/95)	37% (34/92)	49% (46/93)
Proportion with undetectable HIV-RNA at Week 48		30% (28/92)	46% (43/93)

From these results, it can be concluded that the proportion of patients at 24 weeks reaching undetectable HIV-RNA levels was higher in the ritonavir containing regimens (treatments B and C) and the difference with the group receiving treatment A was significant. At 48 weeks there is a significant difference (p = 0.003) in the detectable RNA levels in favour of the triple regimen.

The viral response was found to be higher in patients with lower baseline viral load.

The proportion of patients showing virological failure for patients who had detectable RNA at baseline is presented in the following table:

	Treatment A	Treatment B	Treatment C
Week 12	57% (54/95)	28% (26/92)	32% (30/93)
Week 24	68% (65/95)	45% (41/92)	39% (36/93)
Week 48		46% (42/92)	39% (36/93)

The proportion of patients on the full ritonavir dose decreased from 71 % (140/197) at week 4 to 57 % (112/197) at week 12, to 49 % (97/197) at week 24 and to 36 % (70/197) at week 48. The percentage of patients who discontinued ritonavir permanently was 31 % and 34% had to reduce the protocol full-dose at week 48.

With respect to CD4 cell counts, the best response as measured by mean changes from baseline was observed with ritonavir treatment regimen. However there was no difference between the treatment arms at week 12 with respect to changes in CD4 percentage.

Overall the results suggested that the viral response to ritonavir combination therapy was not durable up to week 48 in the NRTI experienced PI naive patients with less advanced HIV disease. The majority of patients in the ritonavir treatment arms did not achieve undetectable levels at week 48. The 96-week data, submitted post authorisation, seemed to confirm that the viral response to triple regimen did not seem to sustain but the CPMP had some concerns with respect to the methodology of the study which prevented definitive conclusions with respect to durability of therapeutic effect.

As part of the follow-up measures, the results of PACTG studies 366, 345, and 354 were provided. The results obtained for paediatric patients were in line with previous obtained results, and provided new data with regard to younger children (< 2 years of age).

In trial 366, PI experienced patients responded less to treatment compared to PI naïve patients as was to be expected. Multivariate analyses showed that treatment of infants $\leq$ 2 years of age was statistically significant more likely to result in virological control than treatment of children of > 2 years. No new safety signals were evident relative to the established tolerability profiles of the agents administered in this study.

Trial 345: Efficacy observed at week 48 (viral load < 400 copies/ml) of combination treatment with ritonavir (350 mg/m^2), lamivudine and zidovudine in children between 1 month and 2 years of age was in line with efficacy results found in a previous trial ACTG 338 which evaluated children with a median age of 7.1 years. The safety profile of this combination treatment was acceptable.

Trial 354 was prematurely stopped due to difficulties in patient enrolment. Only 7 women were included, where at least 14 women were planned. However, trial 354 is too small to draw any meaningful conclusions.

Viral resistance

The development of HIV resistance to ritonavir occurred *in vitro* and *in vivo* during treatment. The mutation mechanism was adequately investigated. *In vitro* it was demonstrated that single mutations V82F and I84V of the protease-coding domain exhibited reduced susceptibility to ritonavir.

The potential development of viral resistance in a small number of patients treated with ritonavir monotherapy was investigated throughout 3 phase II studies. Serial genotypic and phenotypic analysis showed that sensitivity to ritonavir declined in a stepwise manner. Initial mutation occurred most often at codon 82 (replacement of valine to usually alanine or phenylalanine).

A correlation seemed to exist between the HIV resistant strain development and a decrease of viral suppression in patients since rebound in HIV RNA levels was observed. However this was observed with doses of ritonavir inferior to the recommended doses and data with 600 mg bid are until now insufficient to conclude on this point.

Safety

The safety profile of ritonavir was established on the basis of the phase III study reports.

No death related to ritonavir was reported.

The analysis reveals that the adverse effects related to ritonavir are mostly digestive system disorders (diarrhoea, nausea, vomiting). With regards to diarrhoea (frequency respectively equivalent to 40% and 60 % in studies M94-247 and M94-245) retrospective subgroup analysis was submitted to assess this common adverse event on the efficacy and pharmacokinetics of Norvir and other relevant co-medications. Results suggested that diarrhoea did not substantially alter the antiviral or immunological activity of Norvir. However, this adverse effect is expected to affect the compliance to the ritonavir medication and thereby will affect the ultimate benefit from therapy. It might affect also the absorption of other medications. Further data should be submitted to determine the clinical relevance and to define the clinical outcome of targeted combination therapies.

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Nutritional disorders, hypertriglyceridaemia and hypercholesterolaemia have also been reported, however, the long-term effect of these findings have not been elucidated. Regarding the nervous system, circumoral paresthesia and peripheral paresthesia have been reported. The percentage of patients who discontinued ritonavir treatment in relation to adverse event experience was 16.8 % (5.9 % in the placebo group) in study M94-247 and 26 % (39 % in ritonavir-ZDV group and 19 % in ZDV group) in study M94-245 respectively. Results revealed that the most commonly occurring events tended to appear within the first days of initiating treatment and were often of limited duration.

The increased risk of adverse events attributed to ritonavir associated with concomitant medications was investigated in study M94-247. Increased frequency of adverse effects related to ritonavir associated with other medications was reported among those for nausea (stavudine), vomiting (ZDV) and circumoral paresthesia (ddC).

Ritonavir led to an increase in serum GGT and ALT although this finding does not appear to be clinically relevant.

Since the retina, renal function and thyroid function were toxicological target organs in animal experiments, the potential for similar effects to occur in clinical studies was monitored. No relevant clinical effects have been reported to date.

As there is no appropriate information of Norvir used on a long-term basis, it is requested that patients should be closely monitored.

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 for the protease inhibitors.

During the post-marketing phase, some adverse events were reported for which a causal relationship with ritonavir could not be excluded. Undesirable effects such as allergic reactions, hepatic disorders, renal disorders, seizure, syncope, postural hypotension and dehydration have therefore been added into the appropriate sections of the Summary of Product Characteristics.

Following reports on adverse effects related to diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus in patients receiving protease inhibitors, the CPMP agreed to introduce an harmonised warning into the Summary of Product Characteristics of all the protease inhibitor products.

With respect to children, the safety database included 337 children together with 53 spontaneous reports over a period of 21 months. The safety profile was similar to that of the known for adults, including gastrointestinal symptoms such as nausea, vomiting and diarrhoea as the most common side effects of ritonavir containing regimens. Post-marketing surveillance data on 53 spontaneous reports from paediatric use did not reveal any safety concerns. The safety update report of study ACTG 338 supported the safe use of the claimed dose of ritonavir in paediatric patients. The high content of ethanol in the oral solution used for stability and solubility reasons was not of concern in paediatric patients.

Based on the results from the bioequivalence studies, the safety profile observed with this new formulation did not differ to the current existing oral solution.

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

Events of special interest

Lipodystrophy

Further to recent 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

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protease inhibitor, was associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Protease inhibitors may also be associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. The data provided did not permit any conclusion about the causality. A class labelling wording was however included into the SPC of all the protease inhibitors products, and further investigation will be performed to better define this adverse event.

Muscle-related reactions

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

Liver impairment in HIV positive patients

Further to the discussions held by the *Ad-hoc Group of Experts on Anti-HIV medicinal products* in November 2001, the CPMP agreed that liver impairment was of increasing concern in HIV positive patients both in the form of adverse hepatic effects in patients with normal liver function prior to antiretroviral treatment (ART) and as regards patients with chronic liver disease treated with ART.
In January 2002 the CPMP requested the MAH for all authorised anti-retroviral medicinal products to conduct a retrospective review of clinical trials and post marketing data relating to the use of their product(s) in patients with hepatic impairment and/or HBV/HCV co-infection. Following review of the submitted responses and discussions held during the CPMP meeting and the Pharmacovigilance Working Party meeting in October 2002, the CPMP adopted a list of questions (including general, product specific and SPC wording recommendations).

The review of the MAHs' responses has essentially confirmed that co-infected patients and patients with underlying liver disorders are at increased risk for adverse events, essentially confined to liver events. Overall, there is a disturbing lack of general and product specific knowledge (e.g. relevant pharmacokinetic data in patients with liver impairment), but there are ongoing activities.
For some of the products still undergoing drug development, the MAHs have confirmed that co-infected patients will not be excluded from participation in the studies. The CPMP stressed that whenever feasible a minimum number of co-infected patients should be included in forthcoming studies in order to provide a reasonable basis for a relevant safety (and efficacy) analysis.
Following the review of responses submitted by all MAHs of antiretroviral medicinal products, a class labelling on "liver disease" has been agreed and implemented in the product information for all antiretroviral medicinal products.

The SPC of Norvir has been reworded in accordance with the CPMP recommendations. Furthermore, in section 5.2, data on AUC-12h derived from HIV infected patients (together with Cmax and Cmin) was added. Extent of exposure to ritonavir in comparison to healthy volunteers, after multiple dosing in subjects with mild and moderate liver impairment (400 mg twice daily) is also provided in section 5.2 of SPC.

4. Overall conclusions and benefit/risk assessment

Norvir was the first representative of a new class called protease inhibitors for the treatment of HIV-infected patients authorised in the European Union

Although additional information has been submitted with regard to chemical and pharmaceutical aspects, the data submitted at time of Marketing Authorisation were acceptable to ensure the quality and the consistency of both oral solution and capsule.

The preclinical programme was considered satisfactory for the use of Norvir in the treatment of HIV-1 infection. Additional toxicology information has been provided to complete the toxicological profile.

The CPMP considered during the review process that, in the light of the currently available data, the provisional overall benefit/risk ratio for Norvir was only favourable as combination therapy.

Consequently, the CPMP, gave a favourable opinion under exceptional circumstances for granting a Marketing Authorisation for Norvir 100 mg* hard capsules and Norvir 80 mg/ml oral solution.
This opinion was based on the beneficial effect of 600 mg of Norvir administered twice daily in combination therapy with nucleoside analogues in patients with advanced HIV disease, as measured by clinical endpoints including a decrease in mortality and disease progression. The applicant agreed to provide final reports of both ongoing phase III studies within a specific timeframe as well as a clinical programme for an expanded investigation of Norvir in combination therapy.

In view of additional data provided, Norvir was shown to be efficacious and generally well tolerated.

With respect to the paediatric population, the requirements of the CPMP Points to Consider in the assessment of New Antiretroviral Products (CPMP/602/95 rev.1) have been adequately addressed. It is considered that there are sufficient data to allow a positive risk/benefit ratio for a 350 mg/m² BID dose of ritonavir oral solution to be used in children aged 2-12 years old.

ACTG 338 and M95-310 supported the virological efficacy of ritonavir in antiretroviral experienced paediatric population, although the durability of the response would have to be defined. The safety profile of ritonavir in children appears similar to that observed in HIV-infected adults.

When reviewing the additional efficacy and safety data provided as part of the specific obligations to be fulfilled post-authorisation, the CPMP considered that the risk/benefit profile for this agent was still favourable and that there were no remaining grounds for maintaining the Marketing Authorisation under exceptional circumstances since all the specific obligations have been fulfilled.

Considering that the soft capsule formulation of ritonavir has been shown to be bioequivalent to the marketed oral solution (even when the soft capsule formulation has reduced ethanol level (12 mg/g) and contains up to 30 % ritonavir crystals) that the clinical benefit of ritonavir at the recommended dose of 600 mg twice daily has already been established and that the new formulation is intended to be used in the same indication with the same dosage recommendations, the CPMP considered the risk/benefit profile of Norvir 100 mg soft capsules favourable. The CPMP therefore issued a positive opinion for granting a marketing authorisation for Norvir 100 mg soft capsules.

The approved indication for Norvir 80 mg/ml was initially the following:
"Norvir is indicated in combination with antiretroviral nucleoside analogue(s) for the treatment of HIV-1 infected patients with advanced or progressive immunodeficiency".

After a number of years of clinical use, the CPMP agreed that the indication of Norvir 100 mg soft capsules and 80 mg/ml oral solution no longer reflected current medical practice as a new antiretroviral class were developed (non nucleoside reverse transcriptase inhibitors). In addition, the knowledge concerning treatment of HIV infection has evolved and supporting data relating to this have been presented. However, it was considered that on the basis of the state of the art, it was necessary to warn prescribing physicians to choose ritonavir for the treatment of HIV-1 infection in protease inhibitor experienced patients based on individual viral resistance testing and treatment history of patients. Hence, the indication for treatment has been reviewed and revised.
In addition although no specific study to support a dose regimen escalation has been performed, the available pharmacokinetic/tolerance data suggested that a dose of 300 mg ritonavir (7.5 ml) BID, as sole protease inhibitor in a combination of antiretroviral therapy, for a period of 3 days and increased by 100 mg (1.25 ml) BID increments up to 600 mg BID over a period of no longer than 14 days may increase the tolerability of ritonavir.

Finally, sufficient clinical experience with ritonavir used as pharmacokinetic enhancer (at low doses of 100-200 mg once or twice daily) to boost the plasma concentrations of other protease inhibitors in HIV-infected adult patients has become available.Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Norvir was favourable in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 year age and older). In protease inhibitor experienced patients the choice of ritonavir should be based on individual viral resistance testing and treatment history of patients.

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