SCIENTIFIC DISCUSSION

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

1. Chemical, pharmaceutical and biological aspects

Composition

The new active substance present in Viracept tablets and Viracept oral powder is the mesylate salt of nelfinavir, (3S, 4aS, 8aS)-N-tert-butyl-2- [(2R, 3R)-3-(3,2-cresotamido)-2-hydroxy-4-phenylthio) butyl] decahydro-3-isoquinolinecarboxamide monomethanesulphonate. The molecule contains 5 chiral carbons and the drug substance is presented as a single isomer.
Viracept tablets are conventional, immediate-release, non-coated tablets containing 250 mg of the new active substance nelfinavir in the form of 292.25 mg of the mesylate salt. In addition, each tablet now contains calcium silicate, crospovidone, magnesium stearate, and indigo carmine (E132). Viracept oral powder is presented in the form of a free flowing, sweetened, flavoured powder.

Each gram of the powder contains 50 mg of the new active substance nelfinavir in the form of 58.5 mg of the mesylate salt. The powder also contains microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, and natural and artificial flavour. The proposed dosing device is a 1.25 ml, high-impact polystyrene scoop. This device was considered not to be ideal and the applicant committed to developing an alternative method of dosage delivery for this form. It was subsequently agreed that the most suitable alternative would be to introduce into the pack an additional 5 g scoop in addition to the 1 g scoop to improve the convenience and accuracy of dosing of the powder for adult patients. This larger scoop can deliver 250 mg nelfinavir.

In order to enhance the palatability of the Viracept 250mg tablet two modifications were introduced. The first was to harden the tablet from 12 kp to 21 kp to reduce disintegration in the mouth. The second change was the application of an aqueous film coating. The Viracept 250 mg film-coated tablet formulation was approved following the initial authorisation for Viracept. This new pharmaceutical form is based upon the 21 kptablet core and involves the addition of a proprietary aqueous film-coat. The film-coated formulation was developed to improve the swallowing of the tablets by patients. The clear proprietary aqueous film-coat that was selected is currently used routinely for the coating of tablets.

Active substance

The synthesis and control of the drug substance was considered robust and the manufacturing process and purification procedures, together with the stereochemical controls applied to the starting materials, effectively control the stereochemical purity of the drug substance.
The analytical methods detailed were considered capable of controlling the drug substance within the specification. The applicant supplied additional information on drug substance and clarification of analytical methods and validation.

Other ingredients

The excipients present are of appropriate pharmacopoeial standard or comply with acceptable in-house specifications. Tablets are packed in high-density polyethylene (HDPE) bottles closed by a heat-seal liner and HDPE cap. The powder is also packed in HDPE bottles closed by a heat-seal liner and polypropylene cap. The film-coated tablets are supplied in HDPE plastic bottles fitted with a HDPE child resistant closure with a polyethylene liner. Adequate information was subsequently provided to demonstrate the compliance with the requirements related to minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

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Product development and finished product

The formulation and manufacture of Viracept 250 mg tablets, by a conventional wet granulation process, is adequately controlled and a product of satisfactory and consistent quality is produced. Wet granulation is also used for the oral powder. This wet granulation is discharged through a coarse screen, and dried through a fluid bed drier. The dried granule is sized using a Fitz hammer mill. A minor change in the manufacture of the tablets (compression with harder force, 21 kp, resulting in harder and slightly less thick tablets) has been introduced during the post-authorisation phase to facilitate the ability of the patients to swallow the tablets.

With respect to the film-coated tablets, the selection of the film-coat was based on the need minimise any impact on the dissolution profile of the currently approved non-coated tablets. The manufacturing is the same as for the non-coated tablets, which are then sprayed with the film-coat. The analytical methods detailed were considered capable of controlling the finished products.

The applicant supplied additional information on the physical characteristics of the finished product and clarification of analytical methods and validation.

Stability

Drug substance

Data have been supplied on eight lots of active substance as primary stability data and on three lots as supporting stability data. Batches are outside specification after 6 months at 40 °C/75 % RH and some batches are outside specification after 3 months at 40 °C/75% RH. The supporting data provided all showed a satisfactory stability up to 6 months at 25 °C/60% RH. Thus the retest date was conservatively set at 6 months with storage below 30 °C, protected from light and moisture. The retest period has been since extended to 18 months in tightly closed containers with the storage remark "Do not store above 25° C".

Finished product

Tablets: Only 6 month primary stability data was available at the time of filing. The primary data is however complemented by a large body of supporting data up to 9-months/1 year. There is no significant trend to a decreasing assay or an increase in the oxidation and hydrolysis degradates, or significant change in dissolution after storage for up to 9 months in HDPE bottles at real-time for zone II in Europe (25 °C/60% RH). The proposed shelf life was 24 months at 15-30°C, but the data provided only support a shelf life of 18 months. Additional stability data were submitted as part of the follow-up measures. These new data supported an extension of the shelf life to 36 months.

Oral powder: Three months stability data (real time and accelerated to the ICH test conditions of 25 °C/60% RH, 30°C/60% RH and 40 °C/75% RH) have been provided on three primary stability batches. Seven-month stability data is provided on a single supporting batch. This batch shows significant degradation after 7 months at 40 °C/75% RH. The stability of the three primary batches seems better. The proposed shelf life was 18 months at 15-30°C, but the data provided only support a shelf life of 12 months. Additional stability data were submitted as part of the follow-up measures. These new data supported an extension of the shelf life to 24 months.

Film-coated tablets: Stability data at 5-± 3°C ambient RH, 25°C/60 % RH and 30°C RH/60 % RH up to 12 months and 40°C/75 % RH up to 6 months have been provided. In summary, the uncoated tablets and the film-coated tablets exhibited equivalent stability, supporting a shelf life of 36 months for both preparations.

2. Toxico-pharmacological aspects

Pharmacodynamics

The antiviral activity of nelfinavir was evaluated *in vitro* only, since no validated animal models are available.The studies evaluated the enzyme inhibitory activity, antiviral efficacy and the development of viral resistance.

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In vitro, nelfinavir was shown to be a selective and potent HIV-1 protease inhibitor with apparent K_i values ranging from 1.2-3.2 nM. The mode of inhibition was competitive. In acute *in vitro* antiviral studies, antiviral efficacy was demonstrated against a number of different HIV strains, ED_{50} values ranging from 10-60 nM. For instance, in a cell protection model, nelfinavir was active against HIV-1 RF and HIV-1 IIB strains, with a therapeutic index of 526 to > 900. In a chronic model of infection, nelfinavir produced a dose-related inhibition of precursor polyprotein p55 (gag) processing to product p24. These data indicated that nelfinavir acts as a protease inhibitor of HIV-1 infected cells.

In an acute HIV-1 infection model, additive to synergistic interactions were observed with nelfinavir in dual or triple combinations with approved reverse transcriptase inhibitors. Studies with nelfinavir and other protease inhibitors were less clear.

Resistance to nelfinavir has been studied in HIV-1 variants selected *in vitro* as well as from patients treated with nelfinavir. The pathway for resistance to nelfinavir is mediated through a substitution of an aspartic acid to an asparagine in HIV protease at residue 30 (D30N). Other mutations have been observed but at lower incidence. The potential for HIV cross-resistance to other protease inhibitors has been explored with nelfinavir. Six clinical isolates containing the D30N substitution showed no change in sensitivity to saquinavir, ritonavir, indinavir or 141W94 *in vitro*. This lack of cross-resistance was confirmed with an HIV recombinant virus containing the D30N substitution; the recombinant virus exhibited a reduced sensitivity to nelfinavir, yet retained full sensitivity to the other protease inhibitors. In addition, in patients previously treated with ritonavir, indinavir and/or saquinavir five of fourteen clinical isolates with reduced susceptibility to one or more of these protease inhibitors were susceptible to nelfinavir. The *in vivo* safety pharmacology programme investigated effects on the central nervous system, gastrointestinal tract, and respiratory and cardiovascular systems. *In vitro* studies were also conducted using various tissues. These studies did not reveal effects that were considered relevant for human safety.

Pharmacokinetics

Absorption and distribution: Absorption after oral administration was demonstrated in rats, dogs, primates and humans. Administration of nelfinavir in the fed state improved absorption. Oral bioavailability was 40-80% in rats and dogs. The protein binding in serum was high (~98%) in rats and humans, over a concentration range of 0.5-25 µg/ml. Using ^{14}C-nelfinavir, a wide tissue distribution was demonstrated in rats, with highest levels in the liver. Brain levels corresponded to ~7x the mean antiviral ED_{95}. In rat foetal tissues, ^{14}C-nelfinavir levels were about 10% of maternal blood levels and in lactating female rats, levels of radioactivity in milk and plasma were similar.

Biotransformation: Nelfinavir is extensively metabolised and metabolism was the main route of elimination in rats, primates and humans. In rats and humans, the major metabolic pathways are qualitatively similar but quantitatively different. In both species, hydroxylation on the benzamide and perhydroisoquinolinyl rings was an important metabolic pathway. However, significant differences were observed for additional pathways, in that humans tended to produce more hydroxy-*t*-butylamide related derivates, whereas in rats, hydroxylation of the thiophenyl ring was predominant. Excretion of drug-related material was almost complete by 48 hours post-dose and was predominantly via the faeces in both the animal species and humans.

Based on the toxicokinetic data submitted, systemic exposure to nelfinavir in the repeat dose toxicity and reproductive toxicity studies was shown to decrease over time, and was generally lower than therapeutic exposure levels in humans. The reason for this finding has not been elucidated, but may be related to reduced absorption and enhanced metabolism. Also when systemic exposure calculations (mean C_{max} and AUC values) were corrected for nelfinavir free fraction, the systemic exposure of test animals was generally below therapeutic exposures of humans. This finding raised a query as to the value of the pre-clinical studies. However, in view of the clinical experience with nelfinavir, this was not considered to be an impediment to the granting of a Marketing Authorisation.

Systemic exposure of the test animals to the metabolite M8 (the main metabolite in humans) was not quantified, but was indicated to be in trace amounts. To facilitate the exposure assessment in the toxicity studies, the applicant has further quantified M8 in the plasma of the animal species during the post-authorisation phase. As M8 was shown to be highly protein bound in all species, the systemic M8 exposure was recalculated based on free fraction as for nelfinavir.

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Toxicology

Single dose toxicity was evaluated in rodents following oral administration of nelfinavir. There were no evidence of treatment related systemic toxicity. Minimum lethal doses were > 500 mg/kg (nelfinavir mesylate) in rats and mice and > 5000 mg/kg (free base) in rats.

Repeat dose toxicity was studied in rats and cynomolgus monkeys after oral administration of nelfinavir twice daily for up to 26 weeks, using dose levels up to 800 mg/kg/d (monkeys) and 1000 mg/kg/d (rats). In rats, the thyroid was the major target organ with the main histopathological changes being follicular cell hypertrophy. The underlying cause has not been definitively determined. The applicant proposed that it might be related to the moderate degree of drug-related hepatic enzyme induction observed in the rat. Regardless of the underlying cause, the species-specific physiological difference in thyroid function between the rat and humans is such that similar effects would not be expected in humans. In the monkey, in which the physiological response to stimulation of the hypothalamic-pituitary-thyroid axis is similar to that in humans, there was no evidence of either follicular cell hypertrophy or increase in TSH levels. This rat-specific finding, which was partially reversible within a short treatment-free recovery period, was therefore not considered to indicate a risk for adverse effects on the thyroid with nelfinavir treatment in humans. Furthermore, there was no clinical indication of effects on thyroid function in humans and no clinically significant alterations in thyroid function tests were observed.

A complete programme of reproductive toxicity studies was conducted. Toxicokinetics in the rat Segment II study demonstrated very low safety margins. In the rabbit Segment II study drug plasma levels were generally below the level of quantitation. There were no adverse effects reported in these studies; however, in view of the low systemic exposure of the test animals there is a query concerning the value of the results. This was not considered to be an impediment to the granting of a Marketing Authorisation in view of the intended therapeutic indication and the warning included in section 4.6 of the SmPC in which the lack of a safety margin in the rat study is acknowledged.

Nelfinavir was shown not to be genotoxic in a full battery of tests. However, a specific consideration was the lack of evaluation of the genotoxic potential of M8. The applicant is in the process of conducting *in vitro* tests for genotoxicity and has committed to supply final reports when available.

Carcinogenicity studies were not completed at the time of the initial authorisation but this was not considered to be an impediment to the granting of a Marketing Authorisation in view of the proposed therapeutic indication. The final report of the 104-week rat carcinogenicity study, which was submitted as part of follow-up measures to be fulfilled post-authorisation, showed an increase in the incidence of thyroid follicular cell hyperplasia, adenoma and carcinoma for male rats given 300 or 1000 mg/kg/day and female rats given 1000 mg/kg/day. This mechanism was probably due to microsomal enzyme induction, and therefore not considered to be relevant to humans.

There were no pre-clinical studies *in vivo* which investigated the potential for toxic interactions between nelfinavir and antiretroviral nucleoside analogues. The applicant did not provide justification for this omission. However, information on the safety of combination regimens has been obtained from the clinical development programme.

Good Laboratory Practice (GLP): All pivotal preclinical studies, except the safety pharmacology programme, have been performed in compliance with GLP requirements.

3. Clinical aspects

Clinical pharmacology

Pharmacokinetics

At multiple dosing nelfinavir plasma concentrations indicate dose proportionality. The pharmacokinetics of nelfinavir has not been assessed in subjects with renal failure. This was considered acceptable given the route of elimination of the product but the lack of data from subjects with hepatic failure makes it necessary to recommend that it should not be used in these circumstances.

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Co-administration with nucleoside analogues, zidovudine, lamivudine, stavudine and didanosine, did not affect the pharmacokinetics of nelfinavir. Although co-administration resulted in a significant change in handling of zidovudine, combination of the two with lamivudine produced favourable clinical results and there is no evidence that the reduced plasma levels of zidovudine led to a clinically significant reduction in antiviral activity in the CNS.

Co-administration with other protease inhibitors demonstrated that saquinavir (as soft gel capsule) had the least effect on nelfinavir pharmacokinetics. However, nelfinavir had a marked effect on saquinavir such that the AUC increased by 392%.

Additional data provided during the post-marketing phase showed that co-administration of efavirenz with nelfinavir increased nelfinavir AUC by 20 % with no change in efavirenz AUC. No dose adjustment is needed when these two substances are co-administered.

Nelfinavir does not appear to induce CYP3A to a significant extent but does have some capacity to inhibit the enzyme. Nelfinavir slowed the conversion of terfenadine to its carboxy metabolite and it has been recommended that the two should not be given concurrently. In co-administration studies with selective inhibitors of CYP3A the applicant considered the effect of ketoconazole on nelfinavir pharmacokinetics to be modest and proposed that co-administration with other selective inhibitors would not necessitate dose adjustment of nelfinavir. It was considered that such interaction could not be ruled out and that the data should be reflected in the SPC. The effects of nelfinavir on these other agents have not been described. In co-administration studies with inducers of CYP3A results indicated that nelfinavir should not be given concurrently with rifampin or other potent inducers of CYP3A as co-administration with rifampin resulted in extremely marked reductions in nelfinavir Cmax and $AUC_{(0\text{-}t)}$. Rifabutin had a less marked effect on these parameters and may be suitable for co-administration provided that the dose of this rifamycin is reduced by at least 50% and patients are monitored very carefully for rifabutin-related toxicities.

Oral contraceptives may not provide reliable contraception during nelfinavir therapy since circulating levels of hormones were reduced during concomitant administration. The effect was most likely due to an increase in glucuronidation of oestrogen and progesterone-like substances. Women on nelfinavir should therefore be advised to use a barrier method of contraception.

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.

A published study, which became available during the post-authorisation phase, demonstrated that although concentrations to methadone and its metabolites were reduced by 29-47 % when it is co-administered with nelfinavir to healthy volunteers, none of them experienced withdrawal symptoms. No dose adjustment is therefore recommended.

Although no specific interaction studies have been performed, the potential risk of interaction between nelfinavir and sildenafil, tacrolimus, and pimozide have been considered. Appropriate statements have therefore been added to the Summary of Product Characteristics.

Bioavailability: It was not possible to estimate the absolute bioavailability of nelfinavir due to the lack of an IV formulation. Nelfinavir was significantly more bioavailable when taken with or shortly after food. Study (AG1343-550) assessed the bioequivalence and relative bioavailabilities of the tablet and powder formulations in the fed, but not fasted, state and showed that the formulations were bioequivalent. Since tablet and powder formulations will be recommended for administration with food, and since it is known that absorption is less in the fasting state, this was considered acceptable.

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Clinical efficacy

In the following studies Plasma HIV RNA was measured by the Chiron bDNA assay, with a cut-off for detection at 500 copies/ml.

Phase II studies

Monotherapy*:* Several Phase II trials demonstrated that nelfinavir monotherapy achieved reductions in plasma HIV RNA but, as with other agents of this type, sustained responses for monotherapy were rarely documented.

Combination therapy*:* Study 509 enrolled twelve patients to receive nelfinavir 750 mg t.i.d., zidovudine 200 mg t.i.d. and lamivudine 150 mg b.i.d.; interim results indicated that 8/11 patients remaining on study had undetectable plasma HIV RNA at week 6 and all had reached this status by week 12. Whereas all continued with undetectable levels to week 20, HIV RNA was measurable at week 24 in three patients.

Study 510 enrolled patients to receive 500, 750, or 1000 mg nelfinavir t.i.d. in combination with stavudine or stavudine alone. At four weeks, decreases in plasma HIV RNA from baseline occurred in all groups but were greater and very similar for the three combination treatments compared with stavudine alone. In all four groups mean and median HIV RNA levels did not change notably between days 21 and 56, after which patients on stavudine monotherapy were assigned to one of the nelfinavir doses. At month 6 of combination treatment, mean HIV RNA was less than at baseline but had increased from day 56 onwards in the 500 and 750 mg t.i.d. groups.

Main clinical studies

Monotherapy*:* One trial (505) with 93 patients treated employed an initial double-blind period of 500 mg or 750 mg nelfinavir t.i.d. or placebo for 4 weeks, after which placebo patients switched to one of the active dose groups. There were significant differences between both nelfinavir treatments and placebo for mean AUCMB (area under the curve of the mean change from baseline curve) plasma HIV RNA and CD4 counts. Numerical superiority for these parameters was seen in the higher dose group (in which HIV RNA showed a mean >1 $\log_{10}$ reduction and 16% of patients had undetectable levels) compared with 500 mg t.i.d. (mean <1 $\log_{10}$ reduction). There were rises in means of HIV RNA for both groups from week 4 onwards and no patients had undetectable levels at 16 weeks. CD4 counts dropped in both groups from 8 weeks onwards.

Combination therapy*:* The demonstration of efficacy for nelfinavir when administered in combination with antiretroviral nucleoside analogues depended on two pivotal studies.

The two pivotal phase III studies were of double blind, randomised, parallel group design. Treatment was given for 24 weeks, with a six month (unblinded) extension period in which nelfinavir was added to the regimens for patients who were previously on antiretroviral analogue therapy only.

In trial **506**, nelfinavir (500 mg or 750 mg t.i.d.) in combination with stavudine was compared to stavudine alone in 308 patients. In trial **511**, nelfinavir (500 mg or 750 mg t.i.d. in combination with zidovudine and lamivudine [ZDV/3TC]) was compared to ZDV/3TC alone in 297 patients. Modifications to the dosage regimens were allowed if toxicity occurred.

In both trials, patients with HIV RNA titres of ≥15,000 copies/ml were enrolled; those in trial **506** were naive to stavudine and proteinase inhibitors and had CD4 counts ≥ 50 cells/mm^3 whereas patients in trial **511** were naive to all antiretroviral treatment and there was no lower limit for baseline CD4 counts. The populations included in the two trials were similar in terms of baseline CD4 cell counts and viral load.

Treatment "switching" was allowed after failure, which was defined as return to baseline for HIV RNA or CD4 on two consecutive study visits following at least four weeks of treatment. A Data and Safety Monitoring Board (DSMB) was responsible for implementing the protocol-defined policy of treatment switching for failed patients.

Efficacy Variables and Analyses*:* The primary efficacy variables were $\log_{10}$HIV-1 RNA and CD4 cell counts. The primary analysis was to be AUCMB (area under the curve of the change from baseline curve) over 24 weeks, assessed by analysis of variance. In the protocols, AIDS defining events, acid dissociated p24 antigen (Ag), CD4%, CD8 count, CD8%, CD4/CD8 and quality of life

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were considered secondary efficacy variables. Plasma HIV RNA was measured by the Chiron bDNA assay, with a cut-off for detection at 500 copies/ml.

The primary analysis population ("protocol specified") excluded data obtained after treatment failure. This is not a preferred approach in confirmatory trials, but intention to treat analyses, including all available data, have also been presented in the dossier.

Results of 16 Week Analyses*:* In both studies, the analyses of HIV-1 RNA AUCMB identified highly significant differences between either nelfinavir-containing regimen (500 or 750 mg t.i.d.) or the control regimen. For both the "protocol specified" and intention to treat populations, the significance levels are quoted as p = <0.0001. There were no significant differences between nelfinavir-containing regimens.

The analyses of AUCMB CD4 counts in trial **506** identified highly significant differences between nelfinavir containing regimens and stavudine (difference between means of approximately 54 cells/mm^3; p = <0.0001 for the "protocol specified" and intention to treat populations). Again, there were no significant differences between nelfinavir-containing regimens. In trial **511**, the difference in CD4 cell counts in terms of AUCMB was 22 cells/mm^3. The overall difference between treatments was non-significant for either analysis population.

In trial **506** mean CD4% increased from baseline in all treatment groups with significant greater changes for either nelfinavir group *vs* the comparative regimen. Counts of CD8 cells increased but percentages decreased in all groups; significantly greater reductions with nelfinavir occurred at certain timepoints. CD4/CD8 ratios increased from baseline in all groups.

Two-thirds of patients had detectable p24 Ag at baseline. Mean p24 Ag levels decreased from baseline in all three groups (but not at all timepoints in the monotherapy group) with a significant difference between combinations and monotherapy at week 16.

Small reductions in Karnofsky scores were seen in all groups but were not thought to be clinically significant. New or recurrent HIV-related events occurred in 2/3 of patients in each group.

In trial **511** CD8 cell counts increased from baseline but percentages decreased in all groups; CD4/CD8 ratios increased from baseline.

Two-thirds of patients had detectable p24 Ag at baseline. Mean p24 Ag levels decreased from baseline in all three groups (but not at all timepoints in the 750 mg nelfinavir group).

Small reductions in Karnofsky scores (quality of life) were seen in all groups but were not thought to be clinically significant. New or recurrent HIV-related events occurred in 2/3 of patients in each group.

The majority of treatment failure events were caused by return to baseline in CD4 cell counts without accompanying failure according to HIV RNA criteria.

In trial **506**, 10% of patients on the 500 mg nelfinavir combination had failed treatment, compared to 13% on the 750 mg nelfinavir combination and 36% on stavudine alone. The analyses of incidence of treatment failure and time to failure identified highly significant differences between treatments (p = <0.001).

In trial **511**, the failure rates were low and not significantly different among treatment groups: 10% of patients on the 500 mg nelfinavir combination had failed, compared to 12% on the 750 mg dose and 11% on ZDV/3TC.

Results of 24-week analyses*:* In both studies, the 24-week analyses confirmed the 16-week analyses.

Results of 52 weeks analysis: All patients in 506 and 511 were randomised to either 500 mg or 750 mg t.i.d. nelfinavir after week 24.

52-week results for study **511** showed that there were significantly fewer relapses in the 750 mg t.i.d. group compared with 500 mg t.i.d. and the estimated time for 25% of patients to relapse was much longer at the higher dose. A by-visit assessment from week 24 onwards showed that the 750 mg t.i.d. group contained a significantly higher proportion of patients with undetectable plasma HIV RNA (approximately 80%) compared with the 500 mg t.i.d. regimen (approximately 60%).

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Since Marketing authorisation, further experience has been gained on the use of Viracept in combination with other antiretroviral agents. Hence, in accordance with current therapeutic recommendations, the indication has been reviewed to use Viracept as part of combination antiretroviral treatment.

Virological data derived from clinical isolates

Genotyping of clinical isolates*:* Plasma HIV RNA was obtained from 58 patients exposed to 3-52 weeks of nelfinavir therapy in studies 503 and 510. In keeping with studies *in vitro*, the predominant genotypic mutation was a D30N substitution, which was stable in all 16 patient isolates tested; other mutations were observed at a lower incidence. Ten isolates, which exhibited a reduced susceptibility to nelfinavir, contained the D30N substitution whereas ten isolates, which lacked this mutation, were all fully susceptible. The appearance of this mutation was accompanied by an increase in the plasma viral load in patients. However, nelfinavir-resistant clinical isolates with the D30N change were susceptible to other protease inhibitors, as were isolates which had additional substitutions known to occur during therapy with these other agents. The L90M mutation associated with phenotypic resistance to other protease inhibitors was rarely found in isolates from nelfinavir-treated patients.

The on-therapy incidence of the D30N substitution was estimated from assay of 16-week samples from 142 randomly selected patients who had received monotherapy in study 505 or combination therapy in study 511. The substitution was detected in 18/32 monotherapy patients, but in only 2/22 and 1/27 on 500 and 750 mg t.i.d. regimens with zidovudine and lamivudine. Mutations associated with other protease inhibitor treatments were not seen in any of the 142 patients.

HIV isolated from patients exposed to other Protease Inhibitors*:* At the time of the initial submission, the applicant had obtained 23 HIV isolates from patients thought to have failed on therapy with one of the other Protease Inhibitors. Of these, 15 contained mutations associated with phenotypic resistance to the inhibitor which had been used in therapy or they showed a significant increase in EC_{90}. Although six isolates contained a single mutation and were nelfinavir-susceptible, seven others contained more than one substitution and showed broad cross-resistance despite the fact that the increments in EC_{90} to nelfinavir were less than for other inhibitors.

The applicant had studied a total of 41 isolates from patients who had failed therapy with regimens containing one of the other PIs and reported that 26/41 demonstrated a significant reduction in susceptibility to the PI which had been in use. Eight of these 26 were susceptible to nelfinavir. However, there are no clinical data as yet which document the response of virus known to be resistant to PI(s) other than nelfinavir subsequent to the initiation of nelfinavir therapy.

Study 515 has provided evidence that about 1/3 of patients who have failed a regimen containing a PI may show a response when the PI component is switched to nelfinavir but the applicant did not have viral susceptibility data to accompany these findings.

Dosage recommendation

The dose of 750 mg tid was selected since it was shown to be superior to the 500 mg tid dose in terms of maintenance of the response. However during the post-authorisation phase, it became apparent that there was a need to improve the compliance. Therefore in addition to the development of a new pharmaceutical form, a film-coated tablet 250 mg, to facilitate the swallowing of the tablets, an alternative dosage regimen (twice daily) was proposed based on the results from study AG1343-542. This multicentre, randomised, open-label phase III study involving 554 HIV positive patients, mostly treatment naive patients aged 13 years and older compared the efficacy and safety of nelfinavir, in combination with stavudine and lamivudine in a BID dose regimen to a TID regimen. In a subset of patients, pharmacokinetics of nelfinavir was similar during BID and TID administration. Trough exposures remained at least twenty fold greater than the mean IC_{95} throughout the dosing interval for both regimens. The clinical relevance of relating *in vitro* measures to clinical outcome has however not been established yet.

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The efficacy results from study AG1 343-542 are displayed in the table below:

Proportion of patients with HIV RNA below LOQ (sensitive and ultrasensitive assays) at week 48				
Assay	**Analysis**	**Viracept BID (%)**	**Viracept TID (%)**	**95% CI**
Sensitive	Observed data	135/164 (82%)	146/169 (86%)	(-12, +4)
	LOCF	145/200 (73%)	161/206 (78%)	(-14, +3)
	ITT (NC = F)	135/200 (68%)	146/206 (71%)	(-12, +6)
Ultrasensitive	Observed data	114/164 (70%)	125/169 (74%)	(-14, +5)
	LOCF	121/200 (61%)	136/206 (66%)	(-15, +4)
	ITT (NC = F)	114/200 (57%)	125/206 (61%)	(-13, +6)

LOCF= Last observation carried forward; ITT = Intention to Treat; NC = F: non-completers = failures

The BID regimen produced statistically significantly higher peak nelfinavir plasma levels versus the TID regimen. Small, non-statistically significant differences were observed in other pharmacokinetic parameters with no trend favouring one regimen over the other. No statistically significant differences between the two regimens in terms of efficacy was observed in a predominantly antiretroviral naïve patient population.

No important differences in safety or tolerability were noted between the BID and TID dosing groups. Although the differences in compliance demonstrated in this study were very small, twice-daily dosage regimes are of considerable advantage to many patients of all ages.

In addition, the pharmacokinetics of BID and TID VIRACEPT regimens were investigated in an open prospective study including 18 HIV infected children aged 2-14 years. Children weighing less than 25 kg received 30-37 mg/kg nelfinavir TID or 45-55 mg/kg nelfinavir BID. Children over 25 kg received 750 mg TID or 1250 mg BID. The C_{min}, C_{max} and AUC_{0-24} were all significantly higher with the BID regimen compared with the TID regimen. In addition, in twice-daily administration, 14 out of 18 (78 %) and 11 out of 18 (61 %) reached C_{min} values of 1-3 µg/ml and C_{max} values of 3-4 µg/ml, whereas in TID administration only 4 out of 18 (22 %) and 7 out of 18 (39 %) reached these values.

However, the main body of evidence on efficacy of a BID-dosing regimen comes from the PACTG Study 377:
This study had 4 arms. One arm included children given Viracept BID or TID, and provides comparative data on viral response for these two dosing regimens in children. Only the data from the Viracept containing arm (n=63) are considered relevant to this report. (TID n=52, BID n=11).

In the arm receiving Viracept with stavudine and lamuvidine, 11 of the children chose to receive Viracept as a BID regimen (55 mg/kg BID up to a maximum of 1500 BID) with the remaining 52 receiving Viracept as a TID regimen (30 mg/kg TID up to a maximum of 1250 mg). The median age of those receiving the BID regimen was 6.5 years and for TID was 7.8 years. This difference in age would not be expected to have a major influence on the results as, with the exception of very young children, nelfinavir exposure (with a TID mg/kg regimen) is similar across different age groups. The fact that the selection process to each arm was based on choice rather than through randomisation, may impact the equivalence of the 2 arms.

The results show that the Viracept BID regimen provided similar, RNA response to the TID regimen. The percentage of children with RNA response was higher at all time points. At Week 12/16, 55% in the BID group had RNA ≤400 copies/ml compared with 44% in the TID group. Corresponding values for HIV RNA suppression (RNA ≤400 copies/ml or at least 2 log decrease from baseline) were 64% vs. 58%. Overall tolerability was similar between the BID and TID regimens, although there was a somewhat higher frequency of at least moderate severity gastrointestinal events and fever with the BID regimen.

PharmacoKinetic evaluation was reported in 25 children (6 on Viracept BID and 19 on Viracept TID). Median nelfinavir AUC (adjusted for 24 hours) was higher in the BID treated patients (92.0 vs. 72.9 mg.hr/l) as was C_{min} (1.86 vs. 1.13 mg/l). Univariate analysis of all patients in the study (all arms) with nelfinavir concentration data (n=38) showed an association of very low (≤0.15 mg/l) nelfinavir levels

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at week 4 with a lower frequency of undetectable RNA at 8 weeks (13% vs. 62%, P=0.019) and week 12 (13% vs. 73%, P=0.003).

Dose switching
The MAH developed a 625 mg Viracept tablet to reduce the number of tablets needed to achieve the recommended daily dose of 1250 mg nelfinavir twice daily from 10 x 250 mg tablets to 4 x 625 mg tablets.

During the development of the 625 mg tablets, the MAH developed two formulations that were tested clinically – V11 and V12. V12 was intended for the market. Both formulations contain the same amount of poloxamer 188 (394.375 mg per tablet), which is an excipient well known to act as a surfactant laxative. The V12 formulation was assessed for bioequivalence against the 250 mg film-coated tablet in study *BP 16766* and was the formulation used in the main clinical study in HIV-infected patients *WV 16789* in which gastrointestinal tolerability was assessed. Limited pharmacokinetic data (trough levels were measured) and viral load measurements were presented from WV 16789.

BP 16766

This was a four-way crossover study in 52 healthy male volunteers who received a single dose of 1250 mg nelfinavir in each dosing period administered as either 250 mg or 625 mg V12 tablets in both fed (810 kcal including 45g fat) and fasted states. ANOVA was used to compare log-transformed nelfinavir $AUC_{0\text{-}inf}$ and C_{max} values for test versus reference in each of fed and fasted states. Split data sets were used due to the statistically significant difference in within-subject variability between the fed and fasted states (CV% $AUC_{0\text{-}inf}$: fed 24.4%, fasted 67.9%; C_{max}: fed 22.2%, fasted 62.6%).

In the fed state, the comparisons based on split data sets indicated that the 625 mg V12 tablet and the 250 mg marketed tablet were bioequivalent with respect to nelfinavir. In the fasted state, the $AUC_{0\text{-}inf}$ and C_{max} ratios for nelfinavir were 73% and 97%, with the respective confidence intervals of [59, 90] and [79.6, 118]. A formal analysis of bioequivalence in study BP16766 with respect to the M8 metabolite only just failed to reach the required limits

WV16789

HIV-infected patients on a stable nelfinavir-containing regimen (with 250 mg tablets) or naive to nelfinavir switched to or commenced ART that included 625 mg V12 tablets at 1250 mg b.i.d. (see further details on the study design below). Blood samples were to be collected on Day 14 (switch patients) and Day 28 (all patients) for the determination of morning trough levels of nelfinavir and M8.

While the mean and median loads among switch group patients did not change or decreased slightly up to day 42, the second tableresults shows that the % with < 400 copies/ml dropped slightly over time. In contrast, the data from new nelfinavir patients (who were mainly ART naïve) showed a drop in viral load that correlated with an increasing proportion at < 400 copies/ml. Based on the cut-off proposed by Pellegrin *et al*., 2002, >80% of subjects in the switch group in WV16789 maintained trough nelfinavir levels above the threshold for efficacy against susceptible strains (0.8 mg/l) at day 28 (two weeks after switching to the 625 mg tablets).

No provision was made in the WV16789 study protocol for the prospective collection of plasma viral samples for the assessment of resistance to nelfinavir.

Despite the poloxamer content of the 625 mg tablet, there does not seem to be an adverse clinical effect on bowel function compared with the 250 mg tablets. In HIV-infected subjects, the data showed no evidence of deterioration in gastro-intestinal tolerance in subjects who switched from 250 mg to 625 mg nelfinavir tablets at the same total daily dose. An initial higher rate of diarrhoea, with a lessening of effect with time, would be expected in the previously nelfinavir naïve subjects, but trial WV 16789 was not designed to measure this effect.

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Clinical safety

At the time of the safety update provided in the initial application 819 patients had received nelfinavir alone and/or in combination, of whom 505 had been treated for at least 6 months. Most patients received at least 1200 mg/day. Data on safety beyond one year were limited to 24 patients. A further 2,300 patients had received variable quantities of nelfinavir as part of the expanded access programme; serious adverse events in these patients were also included in the safety update.

Adverse events *(AEs):* In patients, the commonest AEs were diarrhoea, asthenia and headache. Diarrhoea was almost always considered to be drug-related and usually commenced in the first few weeks on therapy. There may be a dose-relationship for the incidence of diarrhoea (30% at 750 mg t.i.d. and 17% at 500 mg t.i.d in the double-blind trials). Further studies indicate that diarrhoea may be caused by both damage to the epithelial barrier and by secretory changes.
Occasional hypersensitivity reactions to nelfinavir occurred during the clinical programme (*eg.* rash with urticaria).

Serious adverse events (SAEs): Very few of the SAEs reported were associated with nelfinavir by investigators; these events do not point to any specific problems with the drug at this stage.

Laboratory findings: Seven patients were withdrawn from the extension of study 503 due to AEs; six cases involved elevated Liver Function (LFTs) in patients with active HBV. In several instances there were clinical signs of hepatitis (tender enlarged liver), and in all cases with follow-up there were reductions and/or resolutions of SGOT, SGPT and other abnormalities after discontinuation of nelfinavir. One patient was withdrawn from study 504 after 28 days due to 3-4 fold increases in SGOT and SGPT from baseline; levels of both were < 50% of peak at one month after discontinuation.

In addition to the transaminase abnormalities noted above, two patients in study 505 had LFT abnormalities but showed some resolution without discontinuation. There were also seven and five patients in Studies 506 and 511 with abnormal transaminase who did not discontinue therapy; most of these had evidence of HBV infection.

Based on the post-marketing surveillance, the CPMP requested reinforcement of the reference to hepatitis, abnormal enzymes liver and jaundice in the product information.

Other abnormalities reported were increases in glucose to grades 1-2 severity. A similar statement with respect to observations of hyperglycaemia and diabetes mellitus, with occasional ketoacidosis, which has been approved for incorporation into the SPCs of the other protease inhibitors, appears in section 4.4 of the SPC for VIRACEPT.

The following additional adverse reactions have been reported in the post-marketing experience: increased spontaneous bleeding in patients with haemophilia; new onset diabetes mellitus, or exacerbation of existing diabetes mellitus; abdominal pain, abdominal distension and vomiting; hypersensitivity reactions including bronchospasm, fever, pruritis, facial oedema and rash (maculopapular or bullous); pancreatitis/increased amylase.

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

Events of special interest

Lipodystrophy

Treatment with a combination of at least three antiretroviral drugs can induce a characteristic syndrome termed lipodystrophy or fat redistribution syndrome containing peripheral fat wasting (including accentuation of facial folds) and central adiposity. Metabolic disturbances such as hyperlipidaemia and insulin resistance also often appear. PIs were originally believed to be the causal agents. NRTIs have also been implicated. In addition, lipodystrophy has also been observed with protease-inhibitor-sparing regimens. The emerging picture is that of a connection between visceral lipomatosis and protease inhibitors and lipoatrophy and NRTIs correlating with different possible mechanisms e.g. effects on lipoprotein production and adipocyte differentiation. Non-drug factors are

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also of importance e.g. increasing age, duration and severity of HIV infection.
Following evaluation of data submitted by all MAHs of antiretroviral medicinal products, a class labelling, which harmonises the information on lipodystrophy for all three classes of antiretroviral products, has been agreed and implemented in the product information for all antiretroviral medicinal products. The wording presents as much as possible of the presently available knowledge; it gives a description of the condition (although there is at present no clear definition of lipodystrophy), information about causality and surveillance measures. The higher risk of developing lipodystrophy with long-term therapy as well as importance of factors such as age and disease related factors is mentioned.

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 MAH is planning to conduct a study of the clinical pharmacology and safety of Viracept in patients with varying degrees of hepatic impairment (n=20). This study will aim to determine (i) the effects of hepatic impairment on the pharmacokinetics of nelfinavir and (ii) the correlation between nelfinavir levels and the incidence of liver enzyme abnormalities, among patients with hepatic impairment.

Paediatric clinical experience

Results of an interim analysis from Study 524, an open Phase I study in four US centres, were submitted in the initial application. Eligible patients were ≤ 13 years of age and HIV-positive. The study was designed to have two phases of investigation. The single dose phase was planned to enrol up to 24 patients with at least four in each age group as follows:

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I: 7 to 13 years
II: 2 to < 7 years
III: 3 months to < 2 years
IV: < 3 months

The multiple dose phase was planned to commence after completion of the single dose phase for each group. Patients who had participated in the single dose phase and up to 10 additional patients per group were to be enrolled; children continued other antiretroviral therapy while taking nelfinavir at the doses identified. The initial observation phase was 6 weeks, with optional extension to 6 months. Thus, pharmacokinetic data were to be provided from this ongoing study for both the 50 mg/g powder (taken with milk, formula, pudding or water) and the 250 mg tablets in children of 3 months to 13 years.

Relative bioavailability: Comparison of single doses of powder and tablet formulations at 10 mg/kg (five patients) and 20 mg/kg (one patient) in children of > 7 years demonstrated similar plasma concentration-time profiles. Mean t_{max} following tablets or powder was not significantly longer at 20 mg/kg compared with 10 mg/kg. Dose-adjusted powder to tablet arithmetic mean ± S.D. ratios from these data were 1.04 ± 0.39 for $AUC_{(0-\infty)}$ and 0.92 ± 0.23 for C_{max}.

An updated report on study 524 was provided which included some additional pharmacokinetic data. Sixteen were in group I (7-12 years), 22 in group II (2-6 years) and 10 were of less than 2 years but > 3 months of age (group III). However, 37 of the 48 had completed the 6 week multiple dose phase and 22 had reached month 1 of the extension period. Dosing information (tablet/powder and/or mg/kg) was available for 42/48 of these children. Calculations (where possible) of the dose administered in mg/kg indicated that the routine doses were in the range 18-30 mg/kg and that the majority of patients were taking close to 20-mg/kg t.i.d.

Efficacy: Post-baseline plasma HIV RNA levels to at least week 6 were available for 15 in group I, 19 in group II and 3 in group III. For children in groups I and II at week 6, mean and median HIV RNA levels were reduced from baseline by 1.0 log_{10} or more. These parameters were similar to or higher than at baseline for six children in-group III at week 2 and for the three children in this group with results available for week 6.

At the time of the data cut-off, there were only nine children for whom data at the second month in extension were available. There was no trend to an increase in HIV RNA from nadir; changes in mean and median CD4 counts from baseline were somewhat erratic whereas the CD4 % showed a trend to rises from baseline.

Safety*:* The MAH provided a safety update on 32 patients enrolled into study 524. Adverse events were as expected from adult data and from this age group. No child had discontinued due to an AE and drug-related events were rare. No new laboratory abnormalities were known as of the cut-off date. A second updated safety report on study 524 included information on two patients enrolled into the single dose phase and another 26 who entered the multiple dose phase (totals 21 and 48, respectively). Safety data were available for 39 children from an expanded access programme. Diarrhoea had been reported in 1/3 of recipients and one child had been withdrawn due to the problem. Other new information did not change the conclusions drawn previously.

At the time of the first annual re-assessment the MAH submitted an analysis of 48-week data for a phase I/II open label multicentre study of the safety, tolerability and pharmacokinetics of the nelfinavir oral powder formulation in children. However, because of limited data it was considered not possible to define the pharmacokinetic profile in children of less than 3 years. The CPMP, who initially recommended the use in children aged from 2 to 13 years, agreed that the age range should be reviewed and therefore nelfinavir is indicated in children of 3 to 13 years of age.

4. Overall conclusions and benefit/risk assessment

Patients greater than 13 years

The demonstration of efficacy in adults was based on the additional reductions in plasma HIV RNA and, to a lesser extent, on increases in CD_4 counts that resulted from addition of nelfinavir to regimens of one or two antiretroviral nucleoside analogues.

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Data demonstrated that continuation of nelfinavir in combination with zidovudine and lamivudine results in maintenance of responses (as measured by these parameters) after 52 weeks on treatment. From 24 to 52 weeks, it became apparent that the 750 mg t.i.d. dose was superior to the 500 mg t.i.d. dose of nelfinavir. Subsequently, study 542 formed the basis for BID dosage recommendation.
The overall efficacy profile of newly developed 625 mg tablet appears comparable to the 250 mg tablets.The tolerability profile for nelfinavir, as currently demonstrated in the clinical programme suggests that its use is uncommonly accompanied by severe or serious adverse events. Again, the overall safety profile of the 625 mg tablet appears comparable to the 250 mg tablets.
In-vitro data demonstrate that the antiviral activity of nelfinavir is associated with a favourable pattern of drug resistance. Studies with isolates resistant to one or more of the other protease inhibitors have shown that susceptibility to nelfinavir is often retained. Nelfinavir-resistant isolates do not always demonstrate cross-resistance to other protease inhibitors.

Patients less than 13 years
Data regarding clinical efficacy of nelfinavir in patients less than 13 years are limited. Marketing authorisation for use of the tablets or powder in such patients is therefore dependent on the safety and efficacy data that are available for the tablet formulation in adults and on the demonstration of bioequivalence between tablets and oral powder.
The application provided limited data on the safety and pharmacokinetics related to administration of the powder to children of 2 to 13 years, and of tablets to children of 7 to 13 years. However, because of limited data it was considered not possible to define the pharmacokinetic profile in children of less than 3 years. The CPMP, who initially recommended the use in children aged from 2 to 13 years, agreed that the age range should be reviewed and therefore nelfinavir is indicated in children of 3 to 13 years of age. Additional data became available to allow BID dosing in this patient group.
There is no suggestion at present that the safety profile in children is significantly different from that in adults.

Overall benefit/risk assessment

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Viracept remains favourable as antiretroviral combination treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children of 3 years of age and older.

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