SCIENTIFIC DISCUSSION

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

1. Introduction

Current options for the treatment of Human Immunodeficiency Virus (HIV) infected patients consist of nucleoside analogue reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs).

The first category of agents (NRTIs) acts at an early stage in the HIV life cycle by blocking the activity of reverse transcriptase. This enzyme is essential for the conversion of viral RNA to proviral DNA, thus allowing integration into host cell DNA and subsequent viral replication. In contrast, the second group of agents (PIs) acts at a later stage in the viral replication. HIV protease is an enzyme essential for the production of mature, progeny virions. The last group of agents (NNRTIs) acts on the reverse transcriptase enzyme through a different mechanism compared to nucleoside analogues RT inhibitors. NNRTIs bind directly to the HIV RT enzyme and block the RNA dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme catalytic site.

Combination therapy, especially triple regimens, is considered to be the standard of care of HIV infected patients. The antiretroviral agents already authorised within the European Union comprise zidovudine (ZDV), didanosine (ddI), zalcitalbine (ddC), stavudine, lamivudine and abacavir as NRTIs, ritonavir, indinavir, saquinavir, nelfinavir, amprenavir and lopinavir as PIs, nevirapine and efavirenz as NNRTI, and tenofovir disoproxil fumarate (TDF) as nucleoside monophosphate (nucleotide) analogue. For the treatment of HIV infected children, the only available options are lamivudine, stavudine and nelfinavir.

The long-term use of these products is limited by emergence of resistance, by toxicity and inconvenient dosing schedules or formulations. Further therapeutic agents are therefore clearly needed.

The active substance of Sustiva, efavirenz is a new chemical entity representative of the NNRTIs class. Sustiva is presented as hard capsules for oral administration in three different strengths, containing 50 mg, 100 mg or 200 mg of efavirenz, as an oral solution containing 30 mg/ml efavirenz, and also as film-coated tablets containing efavirenz 300 mg or 600 mg.

The approved indication at the recommended dose of 600 mg once daily is the following "Sustiva is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children of 3 years of age and older". Since the proposed dosage strengths for the film-coated tablet form are 300 and 600 mg, it is recognised that the form is mostly intended for adult treatment, although it may also be suited for adolescents and children within the appropriate weight range.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

- **Capsules**

Sustiva is formulated as a conventional hard capsule containing 50, 100 or 200 mg efavirenz and excipients commonly used for this pharmaceutical form. The different strengths are direct multiples or sub-multiples of each other with respect to the ingredients entering in the composition but are distinguished by their size, colour and printing.

Sustiva is supplied in opaque, white high-density polyethylene bottle, with a polypropylene but child-resistant cap, containing 30 capsules (50 and 100 mg) or 90 capsules (200 mg). Sustiva 200 mg hard capsules is also supplied in aluminium foil/polyvinylchloride film blister.

- **Oral Solution**

The oral solution consists of a clear solution of efavirenz (30 mg/ml) in a vehicle of medium chain triglycerides with an antimicrobial preservative (benzoic acid) and a strawberry-mint flavour.

There are no ingredients of animal origin in the product.

This 30 mg/ml oral solution presentation is presented in an induction sealed, opaque, high density polyethylene (HDPE) 200 ml bottle with a two-piece child resistant cap, with each bottle containing 180 ml of the oral solution. An appropriately calibrated oral dosing syringe and a press-in bottle adapter are included in the carton for use by the patient or practitioner after the primary container has been opened. The oral dosing syringe is CE marked and is approved for the intended use.

- **Film-coated tablets**

Efavirenz 300 mg film-coated tablets are white, capsule-shaped tablets and the 600 mg strength are yellow, capsule-shaped tablets. Both strengths of tablets are packaged in either HDPE bottles fitted with child-resistant closures, or in blister packs. Each pack contains sufficient tablets for thirty days treatment.

The ingredients are typical for wet granulated tablets : microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium lauril sulphate, hydroxypropyl cellulose, magnesium stearate, and proprietary film-coatings (Opadry).

The primary packs are round, white, opaque HDPE bottles with polypropylene child-resistant closures or blister packs (comprised of white opaque PVE/PE/Aclar blisters sealed with an aluminium foil lid).

Active substance

Efavirenz is a white to slightly pink non-hygroscopic, crystalline powder. The structure of efavirenz has been adequately proven and the physico-chemical characteristics well described. Concerning the physical aspects of the active substance which may have an impact on bioavailability, there are four physical forms (I, II, III and IV) as identified by x-ray diffraction. Forms I, II and III are polymorphs. Form IV is a non-stoichiometric heptane solvate. Forms II, III, and IV are metastable with respect to form I at temperatures >40ºC and convert to Form I on heating. X-ray diffraction and differential scanning calorimetry (DSC) show that the current synthetic processes yield materials of a single crystalline form (Form I), which remains unchanged throughout the subsequent formulation and manufacture of the finished products. Data concerning efavirenz melting point, solubility, UV spectrum, pKa, and kinetics of efavirenz degradation in solution are described. Efavirenz is a chiral molecule but the enantiomeric purity of efavirenz is adequately controlled during the synthesis. An alternative manufacturing process, implemented during the post-authorisation phase, results in the synthesis of the active substance with the same quality.

Degradation of efavirenz in solution is due to specific acid, specific base and solvent catalysis, and follows first order kinetics over the pH range of 0.6 to 12.8. All physicochemical characteristics of efavirenz were considered in subsequent formulation studies. Bioequivalence studies were carried out with product containing active substance in physical Form I.

Stability studies have confirmed the already-known good solid state and solution stability of efavirenz.

Other ingredients

- **Capsules**

All other ingredients entering in the preparation of the capsules meet pharmacopoeial requirements except for the hard capsules which are controlled according to in-house specifications. Satisfactory European Pharmacopoeia certificates of suitability have been provided, magnesium stearate and gelatine to demonstrate compliance with Commission Directive 1999/82/EC and the Note for Guidance on

Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/1230/98 rev.1). The packaging material is controlled according to relevant specifications.

- **Oral Solution**

Both the medium chain triglycerides and the benzoic acid comply with the current specifications of the Ph.Eur. The flavouring agent complies with an in-house specification.

Statements have also been provided from the suppliers of each excipient stating that all ingredients are of non-animal origin.

- **Film-coated tablets**

A PhEur certificate of suitability (TSE) is provided for the magnesium stearate from the stated manufacturer (R0-CEP 2000-176-Rev 00). An assurance is provided that the lactose is TSE free and that all other ingredients in the products are not of animal origin.

Capsules

- **Product development and finished product**

Efavirenz has a low aqueous solubility and a high permeability and therefore the pharmaceutical development focused on the preparation of a rapidly dissolving dosage form. Efavirenz has favourable chemical stability properties. The portion of efavirenz in the final formulation is high so content uniformity is of no concern with respect to the choice of a hard capsule as the dosage form.

Since the quantities of ingredients are adjusted pro rata to the strength, the manufacturing process selected is similar up to the encapsulation point. The critical step in the manufacture is the wet granulation, which includes the following steps: blending, wet granulating, drying, milling and encapsulating. Results on the validation confirm that the manufacturing process is under control and ensures both batch to batch reproducibility and compliance with standard specifications.

Tests at release are standard and include among others limits for assay, degradation products, and dissolution. These tests should ensure reproducible clinical performance of the product. The specifications for the degradation products at release and end-of shelf-life are supported by the results from batch analysis.

- **Stability of the product**

Stability studies have been performed according to ICH requirements. The capsules are chemically stable in all packaging configurations and under all conditions. At the time of the marketing authorisation, stability results supported a shelf-life of 18 months for efavirenz hard capsules when stored in its packaging and long-term data would be submitted on ongoing basis. Additional data have been subsequently provided and the expiry period is now extended to 24 months. Efavirenz does not need any specific precautions for storage.

Oral Solution

- **Product development and finished product**

Although the product meets the requirements of the Ph.Eur. test of antimicrobial preservative effectiveness both in the presence and absence of the benzoic acid, the presence of benzoic acid has been demonstrated to offer a greater effectiveness against moulds. The need for high efficacy of preservation has been accepted because of the immunocompromised nature of the patient population. A toxicological assessment supports the low oral toxicity of benzoic acid, and therefore its inclusion in this formulation is considered justified.

The manufacturing process involves two main dissolution steps: benzoic acid dissolution and efavirenz dissolution. Scale-up and validation studies confirm that the manufacturing process is well controlled and ensures both batch to batch reproducibility and compliance with standard specifications.

Finished product specifications were adequately justified and are based on current standards, including CPMP and ICH guidelines. Justification for the wider shelf-life limits for efavirenz was provided, although when further full scale production batches have been produced the applicant has undertaken to revisit the shelf-life limits and to tighten or further justify them.

Nine production batches were fully analysed and results show compliance with specifications and batch-to-batch consistency.

Proposed specifications, methods procedures and validation, and batch analysis results ensure consistent quality for this medicinal product.

- **Stability of the product**

Three primary stability batches are being tested and data are available for up to 12 months for the 25ºC/60%RH condition, for up to 6 months at 40ºC/75%RH, and for shorter time periods under more stressful conditions. Although there is a slight trend for decreases in the content of both efavirenz and benzoic acid with time and temperature, results from other conditions support the conclusion that the formulation is stable for the testing period. There was no difference in the results from storage of the bottles in the upright or inverted positions.
Results from supportive batches using an earlier sugar containing formulation in glass and HDPE remain within specifications for 24 months (25°C/60%RH) and for 6 months (accelerated and stressed conditions, HDPE bottles). A proposed expiration period of 24 months is sought by the applicant and can be accepted as the stability data provided confirm the stability of the product is acceptable over 24 months when stored below 30°C.

In the SPC, the indicated shelf-life after first opening is one month. A study on the microbiological and chemical properties of the product conducted over a two month period with daily use of the syringe showed no increase in bioburden and no significant decrease in either efavirenz or benzoic acid content. In a second study, efavirenz 30 mg/ml oral solution was placed into the oral syringe and stored at ambient conditions for seven days. The product remained stable. The claimed in-use shelf-life and storage conditions have therefore been supported.

Film-coated tablets

- **Product development and finished product**

Hard gelatine capsules containing 50, 100 and 200 mg of efavirenz are currently licensed for marketing. With a usual daily dose of 600 mg, the current capsule dosage form requires patients to administer multiple dosage units. Therefore, 300 mg and 600 mg tablets will reduce pill burden thus improving patient compliance. The aim of the formulation development was to develop tablets bioequivalent to the commercial capsules (200mg) with acceptable physicochemical properties, stability, and ease of manufacture.
The manufacturing process of the finished product is divided into nine operations: weighing, high shear granulating, wet milling, wet milling/delumping, fluid bed drying, blending, compression, coating and printing. Each batch is comprised of six granulation sub-batches, which are blended to provide one batch of tablet blend. The core tablets for the 300 mg and 600 mg strengths are prepared from powder blend of the same composition, and the core tablet weight is adjusted to obtain the appropriate dose.

The specifications and associated control methods are relevant to a tablet formulation and are acceptable.

- **Stability of the product**

Three primary stability batches for each strength (300 and 600 mg) were studied, in both pack types, under ICH conditions: 25ºC/60%RH, 30ºC/60%RH, 40ºC/75%RH, 50ºC, and photostability. The results, including the content of degradation products, are well within the agreed specifications. Results from other conditions support the conclusion that the formulation is stable for the duration of

the testing period. Results from supportive batches using earlier formulations and stored in either HDPE bottles and film/foil blisters also remain within specifications for 24 months and for 12 months.

In total, the results support the shelflife and storage conditions as defined in the SPC.

Bioequivalence

- **Capsules**

Different formulations have been used during the clinical development. Although efavirenz is formulated using a wet granulation process, a micronised formulation has been used primarily in clinical studies. In one study, 100 mg and 200 mg capsules manufactured using a wet granulation formulation have been tested against a micronised clinical trial formulation and have been shown to be bioequivalent in terms of AUC. The statistically significant difference in C_{max} is considered of no clinical relevance in terms of either efficacy or adverse events. Similar results have been obtained from another study where bioequivalence, in terms of AUC, is demonstrated for both 100 and 200 mg wet granulation formulations compared to the clinical trial formulation. The bioequivalence in terms of C_{max} has been demonstrated with the 200 mg commercial formulation. Finally, capsules obtained from two different lots of active substance have been compared and are found bioequivalent. The bioequivalence between the formulation intended for the market and the ones used during clinical trials has therefore been demonstrated.

- **Oral Solution**

In developing a new oral liquid formulation using a non-aqueous solvent the applicant performed three comparative bioavailability studies using the commercial capsule as the reference. Two liquid formulations were tested in the first study and it was concluded that, in the fasted state, the extent of absorption was approximately 20% lower when compared to the reference. Therefore, in a second study the liquid formulation was tested using either a 200 or 240 mg dose. The results confirmed that the 240 mg dose was bioequivalent to the reference capsule for AUC but not for C_{max} . Finally the intended for market oral solution was again tested against the commercial capsule. The results confirmed the two earlier comparisons. Therefore it can be concluded that the intended for market oral solution is bioequivalent to the 200 mg reference capsule for AUC but not for C_{max} when administered at the 240 mg dose level tested in healthy adult subjects in the fasted state.

- **Film –coated tablets**

Two human bioequivalence studies were carried out using two different tablet formulations (see the clinical section of this report for further details), containing 5% croscarmellose sodium. In study 266-054 *in vitro* dissolution profiles obtained with tablets and capsules were different whereas human pharmacokinetics of the formulation given as a single dose (2×300 mg tablets) was not significantly different (n=12) from that of the commercial formulation (2×300 mg capsules). The causes for differences in dissolution profiles were then identified and corrected. In study 266-058 the same 300 mg tablet formulation was used as in study 266-054, as well as a 600 mg tablet formulation. *In vitro* dissolution profiles were identical to that obtained with 200-mg capsule formulation. Both 300 mg and 600 mg tablets demonstrated bioequivalence with respect to area under the curve (AUC) but not to C_{max} (n=28). The latter was higher than that of the commercial capsule formulation, which did not confirm the results obtained in trial 266-054. Therefore the formulation containing 5% croscarmellose sodium was not considered for further commercial development. In order to optimise the formulation, the concentrations of the disintegrant (croscarmellose sodium) and the binder (hydroxypropyl cellulose, HPC) were varied. Eight formulations were prepared by varying the concentration of croscarmellose sodium (2.0-5.0%) and HPC (3.2-10.0%), and compared with respect to their *in vitro* dissolution profiles and their pharmacokinetics (in dogs). The tablet formulation containing 4.0% croscarmellose sodium (and 3.2% HPC) showed overall results more similar to the commercial capsule, and was therefore selected for commercial development.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Efavirenz is a benzoxazinone of the non nucleotide reverse transcriptase inhibitors group (NNRTIs), which interrupts the reverse transcription of viral RNA to DNA, a crucial step for HIV replication, by a mechanism of action different from NRTIs. Efavirenz binds directly to the HIV-1 RT enzyme and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Efavirenz is specific for HIV-1 RT and is a mixed-type, mainly non-competitive inhibitor. Efavirenz does not inhibit HIV-2 RT nor eukaryotic DNA polymerase such as human DNA polymerases α, ß, γ and δ.

The antiviral activity investigated *in vitro* reveals that efavirenz is active against a broad range of HIV-1 strains, including clinical strains and zidovudine-resistant mutants. The activity in HIV subtype A has, however not been investigated. The dose required to inhibit the viral replication by 95 % (IC95) ranges between 3 to 25 nM, the higher values referring to ZDV-resistant clinical isolates. Higher IC90 values were observed for clinical isolates that contained RT mutations. The antiviral activity of efavirenz is influenced by protein binding, and inhibitory levels increase approximately by 16-fold in the presence of human serum albumin and alpha-1 acid glycoprotein.

The major metabolites, 8-hydroxy-efavirenz and its glucuronide conjugate, have minimal or no antiviral activity. The IC95s for the wild type virus and the Y181C mutant, which is resistant to several NNRTIs were similar (3 and 6 nM respectively) while for the K103N mutant, which is the most resistant single base pair mutant the IC95 was 100 nM. For double base pair mutants the IC95 values range from 400 nM up to > 3000 nM. Cytotoxicity was observed at concentrations 10 000 fold higher than that of IC90 values.

Limited *in vitro* data indicate a synergistic activity of efavirenz in combination with zidovudine, didanosine and indinavir as it could be expected due to different sites of actions of NRTIs and protease inhibitors (PIs). The antiviral activity of efavirenz has not been evaluated in animal studies *in vivo*.

The safety pharmacology studies showed mild and transient bradycardia and respiratory depression in dogs. In mice, some effects on the central nervous system (e.g. reduced activity, ptosis) were observed at oral doses of 100 mg/kg or higher administered orally.

Pharmacokinetics

The pharmacokinetic profile of efavirenz has been determined using validated testing methods in the species used in the toxicity studies after single and multiple dose administration.

Following single oral administration to rats (10, 40, and 60 mg/kg) and rhesus monkeys (2, 10, 40, 80 and 120 mg/kg) the pharmacokinetic profile of efavirenz is linear in terms of C_{max} while the increase in AUC is more than dose-proportional. On the other hand, in humans, the AUC values are less than dose proportional. The oral bioavailability calculated in rats and monkeys is 16 % and 42 %, respectively.

Administration of multiple doses results in decreased exposure in rats and in rhesus monkeys, suggesting an autoinduction of efavirenz metabolism. This pattern has, however, not been reported in cynomolgus monkeys. The exposure to efavirenz is higher in female than in male rats because of higher metabolic activities in males.

Age-related differences have been observed in the pharmacokinetics of efavirenz in monkeys administered 45 mg/kg/day. AUC values in young animals are lower than those in adults and the difference increases along the 14 days dosing period. In addition, the AUCs in young animals are lower at day 14 (104.7 μM.h) than at day 1 (210.5 μM.h). Since this has not been observed in adult animals, the autoinduction of efavirenz metabolism may only be present in young animals.

Efavirenz is highly bound to plasma proteins, primarily to serum albumin, with a mean free fraction of 0.58 % in rat, 0.57 % in rhesus monkey and 0.25-0.5 % in human plasma.

Efavirenz distributes rapidly and extensively in rats after oral dosing, with high levels found in stomach, duodenum, jejunum and liver. Efavirenz crosses the placenta and is excreted in milk. The concentration of efavirenz in cerebrospinal fluid (CSF) showed dose-dependent increases in one monkey study.

The CSF/plasma ratios ranged from 0.54 % to 0.96 %, which are comparable to the free unbound fraction in plasma in rat and rhesus monkey.

The major isoenzymes involved in the metabolism of efavirenz in cynomolgus monkeys and humans are CYP2B, CYP3A, CYP2B6 and CYP3A4 respectively. *In vivo* and *in vitro* metabolism studies have shown that all the efavirenz metabolites identified in humans are also found in rats and cynomolgus monkeys. The major inactive metabolites identified in the three species are the 8-hydroxy efavirenz and its glucuronide conjugate. Three metabolites have in addition been identified in rats, including a cysteinyl-glycine and a glutathione adduct. The human metabolic profile is qualitatively closer to that in cynomolgus monkeys than in rat. *In vitro* studies using liver microsomes have shown that efavirenz is an inhibitor of UDP-glucuronosyl transferases, CYP3A4, 2C9 and 2C19, and may interact with substances metabolised via these isoenzymes.

The plasma half-life of efavirenz in rats is approximately 0.8 to 1.9 hours compared to more than 40 hours in humans. To optimise exposure and to allow for an acclimatisation period, twice daily dosing after an induction phase with once daily doses has been used in most toxicological studies.

Excretion in urine and faeces is comparable after an oral dose of 75 mg/kg in monkeys. In rats, low doses of 10 mg/kg were primarily excreted in faeces, while after an oral dose of 250 mg/kg urinary excretion increased almost to the same levels as faecal excretion.

From the pharmacokinetic and toxicokinetic studies, it can be concluded that the cynomolgus monkey is the most relevant species for toxicity studies. Higher systemic exposure levels can be attained in monkeys compared with rats and the metabolic profile is similar to that in humans.

Toxicology

The toxicological profile of efavirenz has been studied through appropriate studies conducted in compliance with Good Laboratory Practices.

The doses at which toxicity is evident corresponded to systemic exposure levels comparable or not much higher than the expected clinical levels. Higher systemic exposures were achieved in cynomolgus monkey studies, but margins of exposure at the high dose which was toxic, were at the most 4 to 6 times the expected clinical exposure at the recommended doses. When a no-effect-level (NOEL) could be identified, this corresponded to AUC values equivalent to or lower than in clinical therapy.

The minimal lethal doses were 250 mg/kg in mouse after single intraperitoneal administration and 500 mg/kg in rat after single oral administration.
Repeated dose toxicity studies have been performed in rats up to 27 weeks, in rhesus and cynomolgus monkeys up to 57 weeks. Liver and kidney were identified as the main target organs. In rats treated with doses up to 500 mg/kg/bid, the major cause of death appeared to be associated with nephrotoxicity, which was higher in males compared to females. This toxic effect was time- and dose dependent from 50 mg/kg/bid for males and from 250 mg/kg/bid for females. Nephrotoxicity in rats seemed to be due to the formation of a glutathion adduct via a species-specific metabolic pathway. The lesions would appear to be, at least partially, reversible. In cynomolgus monkeys, some renal findings were reported after administration of high doses of efavirenz for 5 days. However, no renal toxicity was seen in cynomolgus monkeys given doses of efavirenz achieving AUC values 5-times the clinical exposure for 1 year. Based on the long term studies in monkeys and the lack of efavirenz-mediated nephrotoxicity in patients during clinical trials, clinical monitoring of kidney function is not considered necessary.

Efavirenz-mediated hepatotoxicity has been observed in all species and is characterised by increased liver weight and centrilobular hepatocellular hypertrophy probably due to an induction the hepatic enzymes. Minimal biliary hyperplasia was observed in the liver of four of the eight cynomolgus monkeys given efavirenz for 1 year at a dose resulting in mean AUC values approximately 5-fold greater than those in humans given 600 mg/day, but was not observed at a dose resulting in mean AUC values of 1.5-fold.
A 105-week oral gavage toxicity study has been performed post-authorisation, in 5 male and 5 female cynomolgus monkeys, receiving 0, 60 or 150mg/kg/day of efavirenz, followed by a 26 week recovery period. Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the

recommended dose. The observed multifocal biliary hyperplasia was reverted during the 6 months recovery period.

Biliary fibrosis was observed in rats given very high doses of efavirenz (500 mg/kg/day).

In cynomolgus monkeys, increases in ALT activity have been observed after administration of efavirenz doses resulting in AUC values approximately 1.5-fold or higher than the expected human value. In addition a decrease in plasma thyroid hormone levels as well as thyroid follicular cell hypertrophy have been reported. This change is considered to be a result of increased thyroxine clearance and a compensatory elevation in serum thyroid stimulating hormone secondary to hepatic enzyme induction. This finding is likely to be of limited clinical relevance, especially since there has been no findings suggestive on an effect of efavirenz on the thyroid function of patients during the clinical trials.

The toxicity of efavirenz in young animals was investigated in infant rhesus monkeys treated for 1 month starting on day 2 of life. At doses of 30 mg/kg/bid corresponding to AUC values approximately 1-2 fold higher than in humans, efavirenz was well tolerated. Efavirenz was not well tolerated by monkeys administered 45 mg/kg bid. Poor appetite, lethargy, dehydration and/or weakness were observed. Although no new toxic effects were identified, data suggest that young animals are more sensitive than adults. These observations have been taken into account when recommending the use of efavirenz in children

Reproductive and development toxicity have been investigated in rats, rabbits and monkeys. Efavirenz did not impair mating or fertility of male or female rats (doses up to 100 mg/kg/bid), and did not affect sperm or offspring of treated male rats (doses up to 200 mg/bid). The reproductive performance of offsprings born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved at the doses used in these studies are equivalent to or below those achieved in humans given recommended doses of efavirenz.

The only reproductive/developmental effects in rats judged to be related to efavirenz treatment were a slight increase in foetal resorptions in females given 200 mg/kg/day and an increase in pup mortality in dams dosed with 100 or 200 mg/kg/day. Efavirenz was not teratogenic or embryotoxic when given to pregnant rabbits at 75 mg/kg/day, a dose that produced peak plasma concentrations similar to, and AUC values approximately half of those achieved in humans given 600 mg of efavirenz once daily.

A teratogenic effect of efavirenz was observed in cynomolgus monkeys. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given 60 mg/kg/day, a dose resulting in plasma drug concentrations similar to those in humans given 600 mg/day. Anencephaly and unilateral anophthalmia were observed in one foetus, microophthalmia in another, and cleft palate in a third foetus. Owing to suspected embryotoxic and teratogenic effects of efavirenz, the compound should not be used in pregnant women unless clearly necessary as indicated in the relevant section of the Summary of Product Characteristics.

Since toxicokinetic data indicates that efavirenz accumulates in milk of lactating animals and crosses the placenta, appropriate information has been included in the SPC.
Efavirenz is not mutagenic or clastogenic in a standard battery of *in vivo* and *in vitro* genotoxic tests.

Carcinogenicity studies of efavirenz were carried out on monkeys, rats and mice.In cynomolgus monkeys, the lack of a tumourigenic effect was difficult to interpret considering the limited duration of the study (105 weeks) in relation to the lifetime span of the species.

In rat carcinogenicity study, 50 males and 50 females per group, were administered efavirenz at 0, 25, 50, and 100 mg/kg/day during 24 months. Concentrations of the drug in plasma were evaluated in the animals following 6 months of dosing. Efavirenz plasma concentrations in female were 1.4 to 2.9 fold greater than those for male rats. Moreover, the plasma concentrations of efavirenz at all dosages evaluated in the study were below those attained in humans given therapeutic dosages (600 mg/day).

In Mouse carcinogenicity study, 50 ma1es and 50 fema1es per group, were administered efavirenz orally by gavage at 0, 25, 75, 150 and 300 mg/kg/day in 0.5% aqueous methylcellu1ose. The dosage of 300 mg/kg/day was not well tolerated, resu1ting in increased mortality in ma1e and fema1e mice.

From the resultes of the carcinogenicity studies it was concluded that efavirenz is more toxic for females than for male animals. Efavirenz showed to be carcinogenic for female mice, in which an increased incidence of hepatic and pulmonary tumors was observed. There was no threshold for the lung tumour effect in female mice while hepatocellular changes in female mice seemed to increase dose-related. The clinical benefit of efavirenz in human HIV-therapy may justify in continuing its use. However, studies with efavirenz must be continued to clarify the mechanism of carcinogenic characteristics of efavirenz in female mice.

Results from local tolerance studies show that efavirenz is a mild skin and eye irritant.

Environmental risk assessment does not foresee any toxicological risk for the environment with efavirenz.

4. Part IV: Clinical aspects

Capsules

The clinical programme consisted of 26 pharmacokinetic studies including one in children, nine phase II/III clinical trials and 1 paediatric study to support the indication of efavirenz in adults and children. All the clinical trials have been performed according to GCP standards and agreed international ethical principles. The clinical programme intended to evaluate the efficacy, safety and tolerability of efavirenz both in monotherapy and in combination with PIs, mainly indinavir but also nelfinavir, NRTIs predominantly zidovudine and lamivudine but also in some extent with stavudine and didanosine both in antiretroviral therapy naive or experienced patient. Patients with advanced disease, namely with CD4 cell counts < 50 cells/mm^3, and PI or NNRTIs experienced patients have not been included in the clinical programme.

The approved indication is "Sustiva is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children of 3 years of age and older*"*. The once-daily administration regimen may improve the adherence to treatment and add to long-term efficacy.

Oral solution

The recommended dosage for children is derived from that already approved for the hard capsules and the approved indication is: "antiviral combination treatment of HIV-1 infected adults, adolescents and children 3 years of age and older, who are unable to swallow the hard capsules".

The clinical development focused on the demonstration of the bioequivalence between the oral solution formulation and the previously authorised hard capsules. Three bioavailability studies in healthy adult volunteers and one open label paediatric study have been performed.

Film-coated tablets

The clinical development focused on the demonstration of the bioequivalence between the new formulation and the previously authorised hard capsules.

Clinical pharmacology

Pharmacodynamics

Efavirenz is a non-nucleoside reverse transcriptase inhibitor agent which acts through a non-competitive inhibition of HIV-1 reverse transcriptase. As indicated in Part III, efavirenz has *in vitro* a synergistic effect with ddI, ZDV and indinavir.

Early clinical studies have demonstrated the potential for rapid development of clinical resistance when efavirenz was used in monotherapy. Efavirenz is therefore recommended to be part of combination treatment regimens, some of which have been evaluated in terms of efficacy during clinical trials.

The nature and the extent of resistance to efavirenz observed *in vitro* and in patients from clinical studies have been characterised in two early studies.

Mutations associated with efavirenz resistance selected during *in vitro* passage correspond to a lysine-to-asparagine substitution at position 103 (K103N), a leucine-to-isoleucine change at position 100 (L100I), a valine-to-aspartic acid substitution at position 179 (V179D) and a tyrosine-to-cysteine substitution at position 181(Y181C). These mutations have also been detected among isolates from patients during clinical studies where efavirenz was administered as part of combination regimens, on a single basis or in combination with other mutations in the RT gene.

The single substitutions which lead to the highest resistance to efavirenz in cell culture correspond to L100I (17 to 22-fold resistance) and K103N (18 to 33-fold resistance). High level of resistance (> 100-fold) required multiple passages and was associated with multiple mutations.

At the time of the CPMP opinion, the genotypic resistance to efavirenz was evaluated taking samples from clinical studies DMP-003 and DMP-004 which are described in the clinical efficacy section of this document. Study 003 enrolled PI and NNRTI naive patients who received efavirenz + indinavir or indinavir. Study 004 enrolled zidovudine + lamivudine experienced patients who received placebo or efavirenz in combination with NRTIs. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during these clinical studies and was identified as single mutation and in combination with other mutations. Within 30 days of viral rebound in patients on efavirenz containing regimens, 90-95 % showed the K103N mutation. The proportion of samples showing multiple mutations, however, increased with time and at about day 100, two mutations were observed in at least 50 % of the isolates. Prolonged therapy with efavirenz after viral rebound was associated with the acquisition of additional mutations. Substitutions at RT positions 100, 101, 108, 138, 188, or 190 were also observed, but at lower frequencies, and often only in combination with K103N. The phenotypic resistance profile of isolates from studies 003 and 004 was also determined. The data corroborated the findings related to genotypic changes. Thus compared with baseline, isolates at viral rebound showed reduced sensitivity to efavirenz (IC90 increased from 20 to > 300 fold).

Final results of the genotyping analysis were later submitted. In line with previously presented data, K103N mutation was the most frequently observed in patients failing efavirenz-including treatment regimens, appearing in over 90 % of the patients in the three studies. K103N mutation was also identified at baseline in one patient from study 003. V108I and P225H mutations were also observed frequently, but predominantly in viral genomes which also contained other NNRTIs resistance mutations. V106A, Y181C or Y188C mutations, which have been associated with resistance to other NNRTIs were rare in the patient samples either before or after exposure to efavirenz.

Cross resistance profile for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution conferred loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from peripheral blood monocyte cells (PBMCs) of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross resistance between efavirenz and protease inhibitors is low because of the different enzyme targets involved. The *in vitro* activity of efavirenz was not affected by mutations associated with protease inhibitors resistance.

Efavirenz mutation was further characterised based on 55 sequences, representing 29 patients failing efavirenz and nelfinavir combination therapy. The results suggested that nelfinavir therapy contributed in part to the evolution of resistance patterns leading to treatment failure.

The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target enzyme and the different mechanism of action. Published information supported this finding. Furthermore, some information obtained *in vitro* using PMBC-derived clinical isolates (studies DMP-003 and DMP-004) were provided. K103N mutant variant which is resistant to NNRTIs showed

no increased resistance to ddC, lamivudine and ZDV. A slight increase in resistance to ddC was observed for isolates containing viruses with several mutations of unknown linkage in the RT gene. For a single isolate with a virus population containing K103N, E138K, and Y188L mutation of unknown linkage, a larger increase in resistance to ddC was observed.

Pharmacokinetics

Capsules

The pharmacokinetics profile of efavirenz was determined in 20 studies performed in healthy volunteers, 5 in HIV infected patients and one in paediatric population. Non-compartimental analysis was undertaken in most cases. In addition three population analyses were provided in two reports one on the combined data from sixteen Phase I studies, one on the combined data from 5 Phase II studies, and one on the Phase II study in paediatric HIV infected patients.

Absorption and distribution

Efavirenz exhibited a linear pharmacokinetic behaviour, but for single doses up to 1600 mg there was a less than proportional dose-related increases in C_{max} and AUC which could suggest a decreased absorption. After single or multiple doses administration, peak efavirenz plasma concentrations were achieved by 5 hours. Following multiple dosing, the steady state plasma concentrations were reached in 7 days. The rate of absorption was not rapid based on the T_{max} values. The low water solubility of efavirenz probably led to a slow dissolution rate in the gastrointestinal tract and the relatively long time to peak concentrations might be a function of the dissolution rate. Other data using liquid-filled capsules in which efavirenz was in solution showed a similar time to T_{max} suggesting that intrinsic properties of the substance are primarily controlling absorption rather than formulation factors.

No chronopharmacokinetic effect was reported with efavirenz and therefore there was no clinically significant difference as to whether healthy volunteers received multiple doses of efavirenz (400 or 600 mg) either in the morning or in the evening.

The absolute bioavailability of efavirenz has not been determined due to the lack of an adequate intravenous formulation.

Food effect on capsules: In healthy volunteers, meals of normal composition had no relevant effect on the bioavailability of efavirenz when administered at the dose of 100 mg twice a day for 10 days with meals. The rate and the extent of the absorption of efavirenz were however increased (> 50.0 %) when given with a high fat meal (4480 kilojoules, 69 % as fat), after a single dose of 1,200 mg. The current recommendation to administer efavirenz with or without food as indicated in SPC, was however clarified during the oral presentation considering that there was no food restriction during the clinical trials, and that the flexibility in dosing might enhance adherence. Upon the request of the CPMP, the effect of food on the pharmacokinetic parameters have been further evaluated as part of the follow-up measures to be submitted after marketing authorisation. Further study strongly points to an increase in exposure to efavirenz of about 25 to 30% (in mean values of Cmax and AUC) when administered concomitantly with meals, as compared to the fasted state.
Food effect on oral solution: The results from a study performed in healthy volunteers to determine the effect of food on the bioavailability of efavirenz oral solution, shown that the geometric mean ratios for natural log transformed Cmax, AUCT, and AUC were 43 %, 25 %, and 30 % increased in the fed state as compared to the fasted state, with 90% CI for all three parameters above the upper limit of 125% respectively, after the high-fat/high-calorie meal compared to the fasted state. These results are consistent with previous findings in similar food interaction studies with the other oral formulations of efavirenz. Also consistent with findings from studies with other formulations is the increase in the frequency of commonly occurring adverse events, such as those usually referred to as NSS, in subjects dosed after a standard high fat meal.
Overall, the results from this study confirmed that there is a significant effect on the pharmacokinetics of efavirenz when administered simultaneously with food, either with a high fat/high calorie meal or a normal fat/normal calorie meal as compared with administration in the fasted state.

Efavirenz was highly protein bound, over 99 %, mainly to human serum albumin. In HIV-1 infected patients who received efavirenz 200 to 600 mg once daily for at least one month, CSF/plasma concentration was 0.0069 (range 0.0026 – 0.0119) at different collection time-points. This proportion represented approximately 3-fold of the free fraction of efavirenz in plasma.

Metabolism

As demonstrated during *in vitro* and *in vivo* studies, efavirenz was metabolised by the cytochrome P450, especially CYP 2B6 and to a lesser extent CYP3A4 to oxydative inactive metabolites. The following metabolites were identified in humans: 8-hydroxy efavirenz glucuronide cyclopropanol (M1), 7-hydroxy efavirenz sulfate (M7) and 8-hydroxy glucuronide (M14). Efavirenz was also shown *in vitro* to induce both CYP2B6 and CYP3A4 and therefore to induce its own metabolism. The AUCs were approximately 8-10% lower following 20 days of dosing as compared to AUCs after 10 days of dosing. Efavirenz was also an inhibitor of CYP2C9, 2C19 and 3A4 and therefore pharmacokinetic interactions of clinical relevance could be expected.

Elimination

Clearance of efavirenz following single oral dose was estimated to be 4.3 l/h in the population analysis consisting of healthy volunteers data and increased to 11 l/h after multiple dosing. The long elimination half-life ($t_{1/2}$) that was observed at steady state in healthy volunteers (40 to 55 hours) supported the recommended once daily administration. The elimination pathway for efavirenz was mainly through the faeces. The majority of the compound was recovered in faeces as the 8-hydroxy glucuronide. Less than 1 % of an oral radiolabelled of 400 mg was excreted in urine as unchanged efavirenz while approximately 14-34 % of the dose was recovered in the urine.

The pharmacokinetics of efavirenz in HIV infected adult patients were similar to those observed in healthy volunteers.

Special populations

The pharmacokinetic profile of efavirenz has not been established in patients with renal dysfunction and in the elderly. Appropriate recommendations have therefore been included in the SPC to reflect the lack of data.

Preliminary results from a study involving subjects with chronic liver disease (Child Pugh Grade A and B) showed a reduction in efavirenz C_{max} and an increase in the unbound fraction compared to the control group. Although no effects on the AUCs were noted, these findings suggested some alterations in efavirenz absorption, distribution and elimination in subjects with liver disease compared to healthy subjects. Considering the extensive CYP 450-mediated metabolism of efavirenz and the limited clinical data, it is recommended that patients with mild to moderate hepatic impairment should be cautioned and monitored as reflected in the SPC. However, efavirenz is contra-indicated in severely hepatic impaired patients (Child Pugh Grade C hepatic impairment).
The steady-state pharmacokinetics of efavirenz in HIV-1 infected patients on stable antiretroviral regimens containing efavirenz, and having selected degrees of hepatic impairment or normal hepatic function, is ongoing.

The pharmacokinetic profile in children aged 3 years and over was evaluated in study ACTG382 which is further presented in the clinical efficacy section of this document. In 48 paediatric patients receiving the equivalent of a 600 mg dose efavirenz, after adjustment of the dose for body size based on weight, the following parameters were defined at week 2 of treatment:

Steady state C_{max} equivalent to 14.21 ± 5.79 µM; steady state C_{min} equivalent to 5.58 ± 4.12 µM and AUC was 218.3 ± 103.7 µM.h. (following 600 mg once daily dose in adults, these parameters correspond to 12.9 µM, 5.6 µM and 184 µM.h, respectively). The pharmacokinetics of efavirenz therefore appeared similar in children to adults after correction for body size.

The population analysis showed that Black race resulted in changes in CL/F that were not clinically significant. These analyses showed that the Asian/Pacific islanders race (3 subjects involved in the population analyses) is associated with a reduction of CL/F by 46 % and therefore an adequate statement has been included into the SPC to reflect the potential higher exposure of efavirenz in this

group of patients. In addition, the gender appeared to have no impact on the pharmacokinetics of efavirenz.

The relationship between plasma concentration and effect was based on data obtained from clinical studies DMP-003 and DMP-004 in which HIV infected patients received efavirenz alone and in combination with indinavir. A clear concentration/effect relationship was supported so that patients reaching C_{min} levels of greater than 3.5 μM had a higher probability of treatment success. The population analysis including data from 419 HIV infected patients estimated that CL/F was 10.3 l/h in the typical patient receiving a 600 mg dose and suggested a trend for heavier patients to have lower steady state trough levels. Weight and dose were included as covariants in the final models.

Interactions

Considering that HIV infected patients are frequently subject to multiple therapies, that efavirenz has the potential to induce CYP 3A4 and to inhibit some CYP450 isoenzymes, an extensive interactions programme has been conducted. The main findings from the interaction studies are displayed in the tables below:

Medicinal products indicated in the same indication

	Co-administered substances		**Dose**	**Efavirenz dose**	**C_{max}**	**AUC**
Effect on efavirenz pharmacokinetics	***Indinavir***	Patients	800 mg q8h x 14 days	200 mg x 14 days	↔	↔
	Nelfinavir	Healthy	750 mg q8h x 7 days	600 mg x 7 days	↔	↔
	Ritonavir	Healthy	500 mg q12h x 8 days	600 mg x 10 days	↑ (14%)	↑ (21%)
	Saquinavir soft capsules	Healthy	1200 mg q8h x 10 days	600 mg x 10 days	↓ (13%)	↓(12%)
Effect of efavirenz on the pharmacokinetics of co-administered substance	***Indinavir***	Patients	800 mg q8h x 14 days	200 mg x 14 days	↓ (16%)	↓ (31%)
	Ritonavir	Healthy	500 mg q12h x 8 days after morning dose after afternoon dose	600 mg x 10 days	↑ (24%) ↔	↑(18%) ↔
	Nelfinavir Metabolite AG-1402	Healthy	750 mg q8h x 7 days	600 mg x 7 days	↑ (21%) ↓ (40%)	↑(20%) ↓ (37%)
	Saquinavir soft capsules	Healthy	1200 mg q8h x 10 days	600 mg x 10 days	↓(45-50%)	↓ (62%)
	Lamivudine	Patients	150 mg q12h x 14 days	600 mg x 14 days	↔	↔
	Zidovudine	Patients	300 mg q12h x 14 days	600 mg x 14 days	↔	↔

Results from study DMP 266-104, and population pharmacokinetic analysis on data from studies 266-003, -006, -020 and -021 have shown that, in healthy volunteers, efavirenz induced an increased indinavir clearance with a reduction in indinavir C_{max} and AUC by approximately 5-29 % and 33-46% respectively. The Ctrough was decreased on an average by 39-57%. Similar differences were observed in HIV-infected patients receiving indinavir with efavirenz compared to indinavir alone. These observations support the existence of highly significant, efavirenz dose-independent, induction of indinavir oral clearance by concomitant efavirenz administration. Also, they would suggest that the daily dose of indinavir should be increased when administered with efavirenz. In clinical trials with efavirenz, the indinavir dose was increased to 1000 mg every 8 hours from a standard regimen of

800 mg every 8 hours. However, a concern was raised by the CPMP on the suggested indinavir dose adjustment recommendation in the light of high inter-individual variability. In addition, *post hoc* subgroup analysis in study –006, suggests that the indinavir + efavirenz combination in naïve (or not heavily pre-treated) patients with high viral load or low CD4+ count at baseline may be less effective than typical first-line HAART (indinavir + zidovudine + lamuvidine). Hence, it is considered that although the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz and indinavir. In line with best practice principles, aiming to guarantee long-term effectiveness of anti-HIV treatment, it is questionable if regimens containing both efavirenz and indinavir fulfil this objective, if used as initial treatment for HIV-infected patients. These observations are reflected in the relevant section of the SPC. Efavirenz had a significant effect on saquinavir soft capsules pharmacokinetics whereas saquinavir had a small effect on efavirenz pharmacokinetics, as indicated in the table. Although the combination was generally well tolerated, the co-administration of efavirenz with saquinavir soft capsules, as the sole protease inhibitor is not recommended.

When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir twice daily shown similar lopinavir plasma concentrations as compared to lopinavir/ritonavir 400/100 mg twice daily without efavirenz. Appropriate recommendations have been included in the SPC.

Although efavirenz decreases the C_{max}, AUC and C_{min} of amprenavir by approximately 40% in adults, when amprenavir is combined with ritonavir, the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir.
Appropriate dosage adjustments have been included in the SPC. Recommendations when efavirenz is given in combination with amprenavir and nelfinavir, are also provided.Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended.

Since the combination of nelfinavir with efavirenz was well tolerated, no dosage adjustment is recommended when both substances are co-administered. In contrast, although efavirenz and ritonavir caused seemingly clinically insignificant changes in the pharmacokinetics of either products, the combination was not well tolerated and was associated with a higher frequency of adverse events (e.g. dizziness, nausea, paraesthesia, elevated liver enzymes). A clinical study aiming to evaluate the efficacy and safety of the combination is ongoing as presented in the clinical efficacy section of this document. Considering the different metabolism pathway, no clinically significant interactions were expected when efavirenz was co-administered with NRTIs. No formal interaction study has been conducted between ddI and efavirenz. In addition, experience of combined treatment with ddI is limited and this is therefore reflected in the SPC.
The potential interactions between efavirenz and other NNRTIs have not been evaluated.

Other medicinal products

	Co-administered substance	Population	Dose	Efavirenz dose	*Cmax*	AUC
Effect on efavirenz pharmacokinetics	***Rifampicin***	Healthy	600 mg x 7 days	600 mg x 7 days	↓ (20%)	↓ (26%)
	Azithromycin	Healthy	600 mg single dose	400 mg x 7 days	↔	↔
	Clarithromycin	Healthy	500 mg q 12 h x 7 days	400 mg x 7 days	↑ (11%)	↔
	Fluconazole	Healthy	200 mg x 7 days	400 mg x 7 days	↔	↑ (16%)
	Famotidine	Healthy	40 mg single dose	400 mg single dose	↔	↔
	Mylanta DS	Healthy	30 ml single dose	400 mg single dose	↔	↔
	Ethinyl oestradiol	Healthy	50 µg single dose	400 mg x 10 days	↔	↔
Effect of efavirenz on the pharmaco-kinetics of co-administered substance	***Azithromycin***	Healthy	600 mg single dose	400 mg x 7 days	↑ (22%)	↔
	Clarithromycin ***14-OH metabolite***	Healthy	500 mg q 12 h x 7 days	400 mg x 7 days	↓ (26%) ↑ (49%)	↓ (39%) ↑ (34%)
	Fluconazole	Healthy	200 mg x 7 days	400 mg x 7 days	↔	↔
	Ethinyl oestradiol	Healthy	50 µg single dose	400 mg x 10 days	↔	↑ (37%)

Based on these results, with the exception of rifampicin, there are no clinically relevant changes in efavirenz pharmacokinetics by any of the studied substances, further confirming the major involvement of CYP2B6 and the minor involvement of CYP3A4 in the elimination of efavirenz. The reduction in efavirenz AUC, C_{max} and C_{min} by rifampicin is likely to be relevant as it may increase the possibility of viral resistance development. As a result, an increase of the dose of efavirenz to 800 mg is recommended when co-administered with rifampicin. Efavirenz induced the CYP3A4 mediated metabolism of clarithromycin to its active metabolite. The increase in ethinyl oestradiol levels was suggested to be related to an inhibition of CYP3A4 although other mechanisms might be involved. The relevant information has been appropriately reflected in the SPC.

Potential interactions with efavirenz have been further evaluated during the post authorisation phase. Efavirenz appeared to reduce rifabutin C_{max} (approximately 30 – 40 %), AUC (approximately 40 – 50 %) and to increase clearance (approximately 70 – 100 %). These data suggest that the daily dose of rifabutin should be increased by 50 % when administered with efavirenz and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with efavirenz. Although relevant information has been included in the product information, the CPMP considered however that this interaction needs to be further discussed.

Convulsions have been observed rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels. Based on this finding a precautionary statement have been included in the product information for patients on therapy with anticonvulsant medications and for patients with a history of seizures.

With regard to antidepressant drugs, the lack of clinically significant pharmacokinetic interaction between efavirenz and paroxetine or fluoxetine, as well as the inductor effect of efavirenz on the metabolism of sertraline, have been highlighted in the the product information.

The absence of clinically significant effects on pharmacokinetic parameters when efavirenz and the H1-antihistamine, cetirizine, are co-administered has been also included in the SPC, as well as recommandation related to co-administration with lorazepam.

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.

Oral solution

During the development of the oral solution of efavirenz, four different liquid formulations were successively tested in terms of comparative bioavailability to the commercially available capsule formulation in three single-dose studies in healthy adult volunteers. The overview of the clinical studies is presented in the table below:

	DMP 266-037	**DMP 266-045**	**ACTG 382**	**DMP 266-101**
Design	single dose 2 period cross-over	single dose 3 period cross-over	Phase I/II open label	single dose 3-period cross-over
Patients	32 males and females	33 males and females	Paediatric patients Cohort II: 19 children	24 male and females
Test products	Oral solution A Oral solution B	Oral solution C (2 dosages 200mg-240mg) Hard capsule 200mg	Cohort I: Hard capsule 200mg + nelfinavir Cohort II: Oral solution C + nelfinavir (stratum 1:3mo.< 2ye. stratum 2:2ye.-8ye.)	Oral solution D (2 dosages 200mg-240mg) Hard capsule 200mg
Conditions	Non-fasting Fasting	Fasting		Fasting

It was concluded that the intended for market oral solution is bioequivalent to the 200 mg reference capsule for AUC but not for C_{max} when administered at the 240 mg dose level tested in healthy adult subjects in the fasted state.

Study DMP 266-037 (Phase I, Single Dose Crossover Pilot Bioavailability Study comparing Two Liquid Formulations of DMP-266 to the Commercial Capsule Formulation)

This was a single dose bioavailability study comparing two different liquid formulations (A and B) of efavirenz to the 200 mg hard capsule. The two liquid formulations were compared in a crossover manner within each of 4 groups with 7 subjects each in the fasted and in the fed state. Results are summarised in the table below:

Single Dose Crossover Pilot Bioavailability Study comparing Two Liquid Formulations of DMP-266 to the Commercial Capsule Formulation (DMP266-037)

	Treatment	No. subjects	Pharmacokinetic parameters (RSD%)					Point Estimator (90% C.I.)				
			tmax* (h)	Cmax** (μM)	AUCT** (μM.h)	AUC** (μM.h)	t1/2** (h)	tmax (h)	Cmax (μM)	AUC (μM.h)	AUCT (μM.h)	t1/2 (h)
Liquid A Vs Capsule	Liquid A fasted Group 1	7	5.0 (4.0-5.0)	3.25 (20.9)	107.4 (49.1)	140.6 (33.4)	95.7 (45.8)	---	---	---	---	---
	Capsule fasted Group 1	7	3.0 (1.0-5.0)	3.06 (33.0)	114.8 (41.2)	146.8 (29.0)	95.1 (41.9)	---	1.12 (0.734-1.72)	0.905 (0.770-1.06)	0.945 (0.844-1.06)	---
	Liquid A fed Group 3	7	3.0 (1.0-5.0)	3.12 (27.1)	152.6 (23.1)	203.0 (26.1)	100.9 (40.2)	---	---	---	---	---
	Capsule fed Group 3	7	4.0 (3.0-5.0)	4.24 (21.4)	157.7 (23.3)	212.3 (21.3)	110.6 (29.5)	---	0.752 (0.667-0.847)	0.969 (0.904-1.04)	0.952 (0.831-1.09)	---
Liquid B Vs Capsule	Liquid B fasted Group 2	7	5.0 (4.0-5.0)	1.92 (34.4)	95.9 (37.5)	124.5 (33.3)	84.1 (51.5)	---	---	---	---	---
	Capsule fasted Group 2	7	2.0 (2.0-4.0)	3.03 (18.8)	115.7 (32.3)	147.9 (29.3)	88.7 (42.5)	---	0.584 (0.420-0.812)	0.799 (0.682-0.936)	0.819 (0.725-0.925)	---
	Liquid fed Group 4	7	4.0 (1.0-12.0)	3.54 (32.5)	134.4 (34.4)	163.3 (34.5)	65.1 (40.2)	---	---	---	---	---
	Capsule fed Group 4	7	4.0 (3.0-12.0)	3.62 (29.6)	139.4 (39.2)	164.0 (33.8)	62.7 (53.9)	---	0.968 (0.729-1.29)	0.984 (0.870-1.119	0.999 (0.961-1.04)	---

(*) Median and range
(**) Mean and RSD%

Study DMP 266-045 (Phase I, Single Dose, Three Period Crossover Study in Healthy Volunteers to Compare the Bioavailability of Efavirenz Administered as a Liquid Formulation to the Commercial Capsule)

This was a single dose bioavailability study comparing two doses of the improved liquid formulation of efavirenz to the 200 mg market capsule. The two doses (200 and 240 mg) of the liquid formulation and the commercial capsule were compared in a crossover in 29 evaluable subjects in the fasted state. The results are summarised in the table below:

A *Phase I, Single Dose, Three Period Crossover Study in Healthy Volunteers to Compare the Bioavailability of Efavirenz Administered as a Liquid Formulation to the Commercial Capsule (DMP266-045)*

		No. subjects	**Pharmacokinetic parameters (RSD%)**						**Point Estimator (90% C.I.)**			
			tmax* (h)	Cmax** (μM)	AUCT** (μM.h)	AUC** (μM.h)	t1/2** (h)	C24 (μM)	Cmax (μM)	AUC (μM.h)	AUCT (μM.h)	C24 (μM)
Treatment	Liquid formulation 200 mg	29	5.0 (3.0-24.0)	1.89 (46.6)	83.6 (41.5)	119 (45.4)	99.7 (37.1)	0.74 (37.8)	---	---	---	---
	Liquid formulation 240 mg	"	5.0 (4.0-8.0)	2.23 (44.8)	100.7 (41.2)	138.4 (41.9)	99.7 (37.0)	0.86 (41.9)	---	---	---	---
	Capsule formulation	"	3.0 (1.0-8.0)	3.68 (28.5)	103.9 (39.8)	140.3 (47.8)	99.6 (31.4)	0.74 (31.1)	---	---	---	---
Comparisons	Liquid 200 vs Capsule	"							0.488 (0.423-0.563)	0.787 (0.721-0.859)	0.843 (0.781-0.909)	0.950 (0.850-1.06)
	Liquid 240 vs Capsule	"							0.571 (0.495-0.658)	0.925 (0.848-1.01)	0.965 (0.894-1.04)	1.07 (0.958-1.20)

(*) Median and range
(**) Mean and RSD%

Study DMP 266-101 (Phase I, Single Dose, Three Period Crossover Study in Healthy Volunteers to Compare the Bioavailability of Efavirenz Administered as an Oral Solution to the Commercial Capsule)

This was a single dose bioavailability study comparing two doses of the intended for marketing oral solution of efavirenz to the 200 mg market capsule (reference). The two doses (200 and 240 mg) of the oral solution and the commercial capsule were compared in a crossover in 23 evaluable subjects in the fasted state. The results are summarised in the table below:

A Phase I, Single Dose, Three Period Crossover Study in Healthy Volunteers to Compare the Bioavailability of Efavirenz Administered as an Oral Solution to the Commercial Capsule (DMP266-101)

		No. subjects	**Pharmacokinetic parameters (RSD%)**					**Point Estimator (90% C.I.)**		
			tmax* (h)	Cmax** (μM)	AUCT** (μM.h)	AUC** (μM.h)	t1/2** (h)	Cmax (μM)	AUC (μM.h)	AUCT (μM.h)
Treatment	Oral solution 200 mg	23	5.0 (3.0-12.0)	2.35 (26.8)	102.5 (29.2)	131.5 (30.3)	85.6 (37.6)	---	---	---
	Oral solution 240 mg	"	5.0 (3.0-12.0)	2.63 (30.0)	116.8 (34.4)	148.2 (35.7)	84.8 (37.0)	---	---	---
	Capsule 200 mg	"	3.0 (2.0-5.0)	3.24 (20.2)	118.0 (23.6)	150.0 (28.2)	88.1 (41.0)	---	---	---
Comparisons	Liquid 200 vs Capsule	"						0.724 (0.665-0.789)	0.892 (0.850-0.937)	0.884 (0.831-0.941)
	Liquid 240 vs Capsule	"						0.785 (0.721-0.855)	0.979 (0.920-1.04)	0.972 (0.926-1.02)

(*) Median and range
(**) Mean and RSD%

Study ACTG 382

The study was initially designed as an open-label, AUC-controlled, multicenter (26 sites) study to determine the pharmacokinetics, safety, tolerability and antiviral activity of once daily efavirenz capsules in combination with nelfinavir in HIV-infected children with a confirmed diagnosis either by virus culture or by PCR in at least two occasions and with plasma levels of above the limit of quantification of 400 copies/ml at screening. The 60 children initially planned in this first design (**Cohort I**) should be ≤ 16 years of age and the initial starting dose of 600 mg, adjusted to body size, was to be further adjusted at week 4 in accordance with the individual tolerability and with the AUCτ levels measured at week 2 in order to attain the target AUCτ levels of 190 to 360 μM.h. The pharmacokinetic parameters were then reassessed at week 6. The initial doses for these patients were calculated based on the "surface rule": Dose = [wt (kg)/70] $^{0.7}$ x 600 mg.

This initial version of the protocol was amended in order to include a second cohort (Cohort II) of 32 children to evaluate a potential efavirenz suspension (liquid formulation C) in combination with nelfinavir. Patients in this second cohort, further stratified into Stratum 1 (≥3 months to <2 years) and Stratum 2 (≥2 years to 8 years), were to be dosed with 720 mg adjusted for size, considering the diminished bioavalability of the suspension relative to the capsules. The dose for nelfinavir for both cohorts was of 20-30 mg/kg tid in patients weighing ≤30 kg and 750 mg tid in patients over 30 kg in weight. The individual doses were adjusted according to changes in body size over time.

With reference to the cohort II paediatric population from study ACTG 382, the results for the mean (SD) values for Cmax, Cmin and AUC at Week 2, and, after appropriate dose adjustments (in order to obtain a previously established target AUC similar to the median AUC in adults), at weeks 6 and 10, were as shown in the following table:

Pharmacokinetic Parameter	HIV-Infected Adults	HIV-Infected Children			
	Capsule (N=35)	Capsule (N=49)	Liquid formulation		
			Week 2 (N=17)	Week 6 (N=6)	Week 10 (N=6)
Cmax, μM	12.9±3.7	14.1±5.8	11.8±5.4	14.1±13.9	12.9±4.8
Cmin, μM	5.6±3.2	5.6±4.1	5.2±4.2	8.7±10.3	4.8±3.8
AUC, μM.*h	184±73	216±102	188±104	261±272	204±92

No statistically significant differences were observed for the pooled data for all ages in terms of CLo [mean (SD) 8.04 (3.29) L/h/m2]. However, when data were stratified in terms of age groups (<5 years and 5 to 8 years), statistically significant differences arose in terms of the mean values for Cmax, AUC and Clo, as shown in the table below, with a greater clearance and lower values for Cmax and AUC in the lower age group. It is suggested that the lack of compliance with the recommended dose may be one of the most relevant explanations to account for the observed variation in AUC. This deficient compliance may result either from missing doses, a fact that must be carefully considered when a once daily dose is recommended, or from difficulties with dosing accuracy with the current formulation, for which a difference of 1 ml may represent more than 10% of the total daily dose.

In trying to overcome the mean 20% lower exposure for the oral solution found in children aged less than 5 years as compared with older children, the applicant proposed a revised dosing nomogram taking into account both body weight, as previously, and age, for which a further 25 to 33% increase in dose is proposed for children below 5 years, as follows:

Body weight (kg)	Efavirenz oral solution (30 mg/mL) dose in mL	
	Age 3 to < 5 years	Age ≥ 5 years
13 to <15	12	9
15 to < 20	13	10
20 to < 25	15	12
25 to < 32.5	17	15
32.5 to < 40	-	17
≥ 40	-	24

This nomogram must be interpreted as such that children starting treatment at ages lower than 3 years will maintain their higher per body weight dosage after reaching the age of 5 until the next body weight level is attained.

Film-coated tablets

Three bioavailability studies in healthy adult volunteers have been submitted.

In general, all three studies were single-dose studies, with single-centre, open-label, non-randomized, crossover designs and adequate wash-out periods (28 days) accounting for the long elimination half-life of efavirenz (52 to 76 hours), except for the pilot study DMP 266-054, in which a 14-day wash-out period was used.

All studies were conducted according to Good Clinical Practice, and the eventual enrolment deviations, which are most pronounced in study DMP 266-108, are not expected to significantly affect the result values for the main pharmacokinetic parameters.

An overview of the main features of the three clinical studies is shown in the table below, with reference to the main results of each study.

Overview of the three clinical studies

Study #	Duration & design	N			Formulations	Results
		Sex (M/F)	Age range	PK evaluable		
DMP 266-054 (James D. Carlson, Pharm D) 16-Jan-1999 to 13-Feb-1999	30 days (two single doses each with a 14-day pharmacokinetic sample collection period)	12/2	19 – 46	12	2 x 300 mg tablets (FN: 0266A-0300A-F-3 x 200 mg capsules	Bioequivalence demonstrated
DMP 266-058 (Krishna Talluri, MD) 12-Jun-1999 to 28-Aug-1999	77 days (three single doses with a 21-day pharmacokinetic sample collection period after each dose and a 28-day washout between doses)	23/6	18 – 46	28	2 x 300 mg tablets (FN: 0266A-0300A-F-B) 1 x 600 mg tablets (FN: 0266A-0600A-E-B) 3 x 200 mg capsules	Bioequivalence not demonstrated
DMP 266-108 (James D. Carlson, Pharm D) 17-Jun-2000 to 15-Sep-2000	77 days (three single doses with a 21-day pharmacokinetic sample collection period after each dose and a 28-day washout between doses)	24/3	18 - 45	21	2 x 300 mg tablets (FN: 0266A-0300A-N-A) 1 x 600 mg tablets (FN: 0266A-0600A-F-A) 3 x 200 mg capsules	Bioequivalence demonstrated

Note: 200 mg reference capsules always with used the commercial formulation.

Study DMP 266-054 was a pilot study, and the results were concordant with the hypothesis that the bioavailability of the 300 mg tablet test formulation (0266A-0300A-F-3) was similar to the commercial hard capsule.

Study DMP 266-058 evaluated the 300 mg tablet formulation 0266A-0300A-F-B and the 600 mg tablet formulation 0266A-0600A-E-B against the commercial 200 mg hard capsules. Bioequivalence was demonstrated for AUC and AUCT according to established CPMP standards, but not for Cmax, for either test formulations. In general, both test formulations showed greater bioavailability than the commercial 200 mg capsules.

A new formulation was developed by reducing croscarmellose sodium from 5% to 4% w/w, in order to reduce the Cmax. Bioequivalence study DMP 266-108 was conducted using this modified formulation for 300 mg (0266A-0300A-N-A) and 600 mg (0266A-0600A-F-A) tablets compared to the 200 mg commercial formulation). Bioequivalence was demonstrated for AUC, AUCT and Cmax, according to CPMP's standards. Detailed discussion of the study DMP 266-108 is shown below:

Study DMP-266-108: A Phase I, Open-Label, Single-Dose, Three-Period Crossover Bioavailability Study in Healthy Volunteers Comparing 300 mg (Formulation 0266A-0300A-N-A) and 600 mg (Formulation 0266A-0600A-F-A) Efavirenz Tablets to Efavirenz Capsules.

A new bioequivalence/bioavailability study was conducted in which tablets made by this modified process were compared to the capsule formulation that is currently being manufactured. This current study evaluated both, a 300 mg (Formulation 0266A-0300A-N-A) tablet strength and a 600 mg (Formulation 0266A-0600A-F-A) tablet strength and compared them to the 200 mg capsule.

The study's design, including the statistical analysis plan, was similar to the one used for study DMP-266-058. As for this later study, a total of 30 healthy subjects were planned for enrolment, however only 27 subjects were enroled at dosing and only 21 subjects were finally evaluable for PK analysis, as one subject failed to return to study premises, three subjects withdrew consent and two discontinued because of AEs (one for vomiting and one for acute mononucleosis and secondary lymphadenitis).

As far as PK results for the main variables are concerned, no carryover or period effects were observed. Descriptive statistics [mean (SD] for most parameters, except median (range) for Tmax and harmonic mean (pseudo-SD) for t1/2] for subjects administered efavirenz capsule and tablet formulations were as presented in the table below:

Descriptive PK results for study DMP-266-108

PK Parameter	300 mg Tablet 2x300mg (Test)	600 mg Tablet 1x600mg (Test)	Capsule 3x200 mg
	N=21	N=21	N=21
Cmax, µM	7.62 (2.26)	8.06 (1.95)	7.50 (2.81)
Tmax, h	3.00 (2.0 – 5.0)	4.00 (2.0 – 8.0)	4.00 (2.0 – 5.0)
AUCT, µM*h	332.57 (116.92)	338.77 (111.37)	326.97 (112.47)
AUC, µM*h	363.28 (124.75)	373.24 (121.73)	359.01 (118.56)
T1/2, h	76.03 (28.46)	78.21 (27.74)	75.81 (29.56)
Clo, L/h	5.78 (1.80)	5.59 (1.74)	5.88 (2.07)

No statistically significant differences were observed between the result values for either of the formulations. The statistical tests were conducted on the natural log-transformed data for Cmax, AUCT, and AUC and observed (non-transformed data) for Clo. For Tmax, the test was conducted using non-parametric methods. As shown in the table below for the 300 mg tablet formulation, the geometric mean ratios for Cmax, AUCT, and AUC were 3.5%, 2.4%, and 1.8% higher, respectively, compared with the capsule formulation. For the 600 mg tablet formulation, the geometric mean ratios for Cmax, AUCT, and AUC were 10.1%, 1.9%, and 3.0%, higher, respectively, compared with the capsule formulation. The 90% CIs for Cmax, AUCT, and AUC were within 80-125% for both tablet strengths.

Analysis of natural log-transformed PK results for study DMP-266-108

Parameter	Tablet	N	Observed data		Log_e-transformed data				
			Capsule (least-square mean)	Tablet (least-square mean)	Capsule (least-square mean)	Tablet (least-square mean)	Difference	GMR (% of reference mean)	90% CI (% of reference mean)
Cmax	300	21	7.49	7.61	1.954	1.989	0.034	103.48	92.73, 115.46
	600	21	7.49	7.90	1.954	2.050	0.096	110.07	98.65, 122.82
AUCT	300	21	321.10	328.37	5.720	5.743	0.024	102.38	96.02, 109.16
	600	21	321.10	325.35	5.720	5.739	0.019	101.94	95.61, 108.69
AUC	300	21	352.95	358.42	5.819	5.836	0.017	101.76	95.95, 107.92
	600	21	352.95	362.16	5.819	5.848	0.029	102.98	97.11, 109.22

The reference (Ref) and test means are least square estimated means (LS Mean) from the ANOVA model. The ratios are the geometric mean ratios (GMRs) for the natural log –transformed values.

The study's safety evaluation shows that, overall, 22 (81.5%) of the 27 subjects reported at least one new-onset adverse events (AE). The AEs most frequently reported in greater than 10% of the subjects included dizziness (13, 48.1%); headache (9, 33.3%); nausea (7, 25.9%); impaired concentration (4, 14.8%); and flu-like symptoms, vomiting, and euphoria (each 3, 11.1%).

This incidence is generally similar to the incidences found in similar studies and there were no apparent differences in the observed incidence of AEs among the three formulations: AEs reported in greater than 10% of the subjects after receiving the 300 mg tablet formulation included dizziness (7, 29.2%), headache (6, 25.0%), and nausea (3, 12.5%); after receiving the 600 mg tablet formulation, the AEs reported in greater than 10% of the subjects included dizziness (8, 33.3%) and headache (3, 12.5%); after receiving the capsule formulation, the AEs reported in greater than 10% of the subjects included dizziness (7, 29.2%) and headache and nausea (each 3, 12.5%).

No clinical laboratory test results were reported as AEs by the investigator.

Seven (25.9%) subjects reported at least one AE of moderate intensity. The moderate AEs included a cut on the third digit of the right hand, acute mononucleosis, lymphadenopathy, finger pain, influenza-like symptoms, headache, myalgia, cystitis, and back pain. Two incidence of headache reported by one subject were considered probably related to study medication; all other moderate AEs were considered unrelated to study medication.

Six subjects discontinued from the study prematurely: three subjects withdrew consent, two subjects discontinued because of AEs (one for vomiting and one for acute mononucleosis and secondary lymphadenitis), and one failed to return to the clinical study unit. No deaths or severe AEs were reported.

As far as AEs of particular interest in subjects receiving efavirenz (rash and nervous system symptoms) are concerned, one subject had a rash on Day 8 of Period 2. The rash was of mild intensity and considered by the investigator to be unlikely related to study medication. Seventeen (63.0%) of the 27 subjects reported a total of 34 nervous system symptoms. Six subjects reported a single occurrence of a nervous system symptom and 11 subjects reported more than one occurrence. Dizziness, the most frequently reported AE, occurred in 29.2% to 33.3% of subjects receiving each formulation. Other nervous system symptoms reported by 10% or more of the subjects after receiving one of the formulations were concentration impaired (14.8%) and euphoria (11.1%).

All 34 occurrences of nervous system symptoms were of mild intensity. Except for one occurrence of dizziness, all nervous system symptoms were considered to be treatment-related.

Clinical efficacy

A total of 9 phase II/III studies and 1 paediatric study were provided to support the indication of efavirenz in adults and children. The clinical programme intended to evaluate the efficacy, safety and tolerability of efavirenz both in monotherapy and in combination with PIs, mainly indinavir but also nelfinavir, NRTIs predominantly zidovudine and lamivudine but also to some extent with stavudine and didanosine both in antiretroviral therapy naive and experienced patients. Double, triple as well as quadruple therapy with efavirenz have been evaluated. Five main studies were presented with the proposed 600 mg dose, of which one was still ongoing and one presented efficacy data evaluable at 48 weeks (study DMP 266-006). Two other controlled studies presented data at 24 weeks and several uncontrolled studies were submitted to support the efficacy.

Final study reports have been later submitted as part of the commitments to be fulfilled post-authorisation.

Dose finding studies

The main objective of the dose selection of efavirenz was to obtain maximum virus suppression and to use the maximal dose tolerated. Initially, the dose of 200 mg was selected based on preclinical and clinical pharmacokinetics data obtained from the early studies. Considering the long $t_{1/2}$ of 40-55 hours, once daily dosing regimen was possible. Since efavirenz administered at the dose of 200 mg showed a good tolerability, higher doses were tested.

Study DMP 266-004 (cohort I-III) was designed to assess the relative efficacy of 400 and 600 mg doses when added to lamivudine and zidovudine therapy in patients with plasma HIV RNA above 2,500 copies/ml. This study enrolled 62 patients who were randomised as follows: ZDV + lamivudine (n = 23), or ZDV + lamivudine + efavirenz 400 mg (n = 22) or ZDV + lamivudine + efavirenz 600 mg (n = 17). At week 16 the efficacy measured by time-to-treatment failure using the HIV RNA plasma levels (limit of detection 400 copies/ml), was greater with the 600 mg dose. The number of patients was however too limited for a reliable statistical analysis. In addition since the protocol was amended several times and individuals receiving the 400 mg dose had higher baseline viral load and lower CD4 cell counts than those receiving 600 mg, it is difficult to draw conclusions. Doses higher than 600 mg were not evaluated in terms of efficacy and safety.

DMP 266-005 was the main dose ranging study to assess the efficacy and safety of efavirenz at the doses of 200 mg, 400 mg and 600 mg in combination with open-label ZDV + lamivudine in HIV infected patients. The design of this study is presented in the section main studies. Overall the results at week 16 were consistent with the superiority of the triple combination regimen including efavirenz at any dose over the double NRTI regimen. The study was not powered enough to detect differences between efavirenz arms. The superiority of efavirenz therapy was shown by the number of patients with plasma HIV RNA < 400 copies/ml and further corroborated by the ultrasensitive assay (limit of detection 50 copies/ml), and greater drops in viral RNA in the efavirenz-containing groups**.** The percentage of patients with undetectable viral load was quite comparable for the three doses. After 16 weeks of treatment all the doses of efavirenz were changed to 600 mg, and the study design was changed (unblinding patients), which makes the interpretation of the results difficult. This study corroborated the effectiveness of efavirenz in combination with two NRTIs.

In the paediatric study ACTG 382, the pharmacokinetics in children was shown to be equivalent to that in adults adjusted for body size based on weight. As a consequence, the recommended dose of 600 mg was adjusted to body size, which was considered to be similar to the 600 mg dose of efavirenz used in adults. For children weighing 40 kg or more, the recommended dose of 600 mg, based on adults in this weight range, was considered acceptable.

Main studies

Nine phase II/III studies and one paediatric study were provided with the submission. All the main studies compared the efficacy of efavirenz-containing regimens to the standard of care at the time. Five main studies were presented with the proposed 600 mg dose, of which one was ongoing and one

presented efficacy data evaluable at 48 weeks (study DMP 266-006). Two other controlled studies presented data at 24 weeks and several uncontrolled studies were submitted to support the efficacy. Final study reports have been later submitted as part of the commitment to be fulfilled post-authorisation.

Efavirenz has been evaluated in double therapy (efavirenz + indinavir/nelfinavir), triple therapy (efavirenz + zidovudine + lamivudine) and in quadruple therapy (efavirenz + indinavir/nelfinavir + 2 NRTIs) in both treatment naive and experienced patients. The overview of the clinical studies is presented in the table below:

	MAIN STUDIES				**PAEDIATRIC**
	DMP 266-005	**DMP 266-006**	**DMP 266-020**	**ACTG 364**	**ACTG 382**
Phase	II	III	III	III	I/II
Design	Multicentre Randomised Double blind Placebo-controlled	Multicentre Randomised Open label Comparative effectiveness and safety studies	Multicentre Randomised Double blind Placebo-controlled	Multicentre Randomised Partially double blind rollover study	Multicentre Open label PK study
Reference	ZDV + LAM	ZDV + LAM + IDV	IDV + NRTIs	NFV + 2 NRTIs	
Test regimen	EFV 200, 400 or 600 mg + ZDV + LAM	EFV + IDV EFV + ZDV + LAM	EFV + IDV + NRTIs	EFV + 2 NRTIs EFV + 2 NRTIs + NFV	EFV + NFV + NRTIs
No of patients	137 (119 M/18 F)	450 (386 M/64 F)	184 (147 M/37 F)	195 (171 M/24 F)	57 (20 M/37 F)
Treatment duration	16 weeks	48 weeks	24 weeks	24 weeks	24 weeks
Planned duration	Open extension phase up to 48 weeks	60 weeks	Open extension phase up to 60 weeks	48 weeks	
Criteria for inclusion	Treatment naive patients HIV RNA > 10,000 copies/ml CD4 cell counts ≥ 50 cells/mm^3 23 to 71 years old	PIs, NNRTIs and LAM naive patients HIV RNA > 10,000 copies/ml CD4 cell counts ≥ 50 cells/mm^3 18-64 years old	NRTIs experienced Patients (≥8 weeks) HIV RNA > 10,000 copies/ml 22 to 64 years old	NRTIs failing PIs and NNRTIs naive HIV RNA > 500 copies/ml 18 to 74 years old	NRTIs experienced > 400 copies/ml NNRTIs & PI naive 3 to 16 years
Baseline characteristics (mean CD4 cell counts and mean HIV RNA	367.2 cells/mm^3 4.72 log_{10} copies/ml	345.3cells/mm^3 4.77 log_{10} copies/ml	325.0 cells/mm^3 4.33 log_{10} copies/ml	388.3 cells/mm^3 3.91 log_{10} copies/ml	845.5 cells/mm^3 4.09 log_{10} copies/ml

EFV=efavirenz; IDV=indinavir; LAM=lamivudine; ZDV= zidovudine

Primary and secondary endpoints

The primary clinical endpoint used in all clinical studies was the percentage of patients with viral load below the limit of detection at defined time-points. The HIV RNA measurement method was the Amplicor assay with a limit of detection of 400 copies/mm^3. In several studies, the Amplicor ultrasensitive assay with a limit of detection of 50 copies/mm^3 was also used in subsets of patients, but never for primary endpoint evaluation.

Secondary clinical endpoints included changes from baseline of plasma HIV RNA and CD4 cell counts. Time to treatment failure was evaluated using the HIV RNA levels**.** Other efficacy measures included changes in clinical status and the new emergence of HIV-related conditions. Quality of life

was also evaluated in most of the studies using the MOS-HIV 30 Health Survey questionnaire, as well as changes from baseline of body weight and of Karnofsky score. The efficacy measurements and endpoints used are in accordance with the CPMP Points to Consider document on antiretroviral medicinal products dated November 1997 and are considered acceptable. It has recently been demonstrated that the lower the nadir of the response in viral load (less than 50 copies/ml) is, the better is the chance for durability of response. The use of the ultrasensitivity assay, in particular in 3 of the pivotal trials, is therefore of great interest for validating the antiviral activity efficacy of efavirenz.

Statistical analysis

Some of the study protocols were amended several times in response to new scientific findings related to sub-optimal therapy and changes in the standard of care, which complicated the interpretation of the efficacy results achieved in the initial trials.

Efficacy was analysed using different statistical approaches: Intention-to-Treat (ITT) population which includes all randomised patients and Efficacy Evaluable (EE) population which includes all patients who meet the efficacy evaluable criteria. Data analyses performed on these two populations included observed data, last observation carried forward (LOCF) and Non Completer = Failure (NC = F). The observed data consist of data for patients reaching a given time point without accounting for failures and drop-outs whereas in the ITT-LOCF the last on-treatment observation is carried forward for patients who do not complete or have missing data at the last study visit.

The NC = F population includes all randomised patients and counting all patients not reaching a given time point as failures regardless of reason for premature discontinuation. Among the populations studied the NC = F was the most conservative and stringent group for efficacy assessment.

Results

Patient population

The demographic and baseline characteristics of the adult patients enrolled were very similar in all the submitted studies. Baseline characteristics were well balanced between the efavirenz-treated patients and the control-treated patients with regards to demographics, viral load and CD4 cell counts. Of the 874 patients randomised or crossover in the sponsor trials, 83 % were male, 63 % were Caucasian and 19 % Black. The median age was 36 years (range17-71) and the median HIV RNA levels was 4.7 $\log_{10}$ copies/ml (range 2.3-6.5 $\log_{10}$ copies/ml). All the studies were conducted in patients with early HIV disease, the median CD4 cell counts being 324 cells/mm^3 (range 9.5-1,234 cells/mm^3). Important groups such as elderly patients, patients with advanced HIV disease, namely patients with CD4 cell counts < 50 cells/mm^3, PI-experienced and NNRTI-experienced patients were excluded.

The paediatric study involved NRTI experienced children from 3 to 16 years of age with plasma HIV RNA > 400 copies/ml.

Studies in adult patients

b) Study DMP 266-006

This was an open-label study due to the complexity of blinding the study medications, which is an understandable shortcoming. The protocol was amended 5 times as a consequence of new scientific knowledge. Initially patients randomised to the efavirenz + indinavir received efavirenz at the dose of 400 mg once a day and indinavir at the dose of 1200 mg tid. These doses were respectively changed to 600 mg and 1000 mg tid. Consequently the size of the different arms increased as well as the observation period. The primary objective was to determine the equivalence between the double therapy efavirenz + indinavir and then the current standard of care indinavir + ZDV + lamivudine based on the proportion of patients with HIV-RNA levels below the limit of detection (< 400 copies/ml). This study was the largest of the main studies, enrolling 450 patients up to the 24 week endpoint. The baseline characteristics were similar between all treatment groups with a plasma HIV RNA approximately 4.77 $\log_{10}$ copies/ml and CD4 cell counts of approximately 345 cells/mm^3.

Results at 24 weeks showed equivalence between the double therapy (efavirenz + indinavir) and the reference therapy (indinavir + ZDV + lamivudine). Of the patients included in the

ITT – NC = F population, 65 % and 56 % for these treatment groups respectively had undetectable viral load (< 400 copies/ml) with an increase in the CD4 cells in the magnitude of 134 and 115 cells/mm^3. In addition the viral response was statistically significant in favour of the triple regimen containing efavirenz arm over the two other arms, with 74.7 % (< 400 copies/ml) and 58.0 % (< 50 copies/ml) of patients having undetectable HIV plasma level using the more stringent analysis. A mean increase of CD4 counts of 129 cells/mm^3 and a mean decrease in viral load of 2.1 log_{10} at week 24 were also demonstrated.

Further results at 48 weeks for the first 450 patients enrolled were submitted which confirmed the results observed at week 24.

The virological response was maintained at week 48 for the efavirenz + ZDV + lamivudine treatment arm both when the 400 copies/ml and the 50 copies/ml limits were considered. The percentage of patients with undetectable HIV plasma level was statistically significant in favour of the efavirenz triple regimen arm compared to the current standard care although this was not the primary analysis for this protocol (71.1 % below 400 copies/ml and 65 % below 50 copies/ml). More patients in the indinavir/ZDV/lamivudine arm discontinued the treatment due to adverse events compared to the two other treatment arms. This might have contributed to the differences in the percentage of patients with undetectable viral load in favour of efavirenz. At 48 weeks 28 patients in total discontinued treatment in the indinavir + ZDV + lamivudine group compared to 10 in the efavirenz + ZDV + lamivudine due to an adverse event. A post hoc logistic regression analysis of the impact of multiple baseline parameters on efficacy was performed based on the responder rates. This analysis demonstrated that there was no correlation between baseline weight, age, sex, race, plasma HIV RNA, CD4 cell counts on efficacy outcome for the efavirenz plus two NRTIs arm. Patients were stratified by baseline plasma HIV-RNA (below and above 100,000 copies/ml) and results demonstrated that the percentage of responders seemed to be independent of the baseline viral load.

Final analysis performed on a subset including 614 patients who had been enrolled at least 48 weeks prior to cut-off has been later submitted. The results are presented below:

Percentage of patients with plasma viral loads below the limit of detection at 48 weeks and change from baseline CD4 cell counts (cells/mm^3)

	Method of analysis	**Efavirenz + indinavir n = 206**	**Efavirenz + ZDV+ lamivudine n = 202**	**Indinavir + ZDV+ lamivudine n = 206**
Viral load below 400 copies per ml	ITT: NC=F	54.0 %	66.7 %	45.3 %
Viral load below 50 copies per ml	ITT: NC=F	47.8 %	61.6 %	40.4 %
Change from baseline CD4 cell counts (cells/mm^3)	ITT: LOCF	177	187	153

ITT :NC = F : Intent to treat population = non completer = failure criteria
ITT : LOCF : Intent to treat population = last observation carried forward criteria

The response rate at 48 weeks was in line with the results reported at 24 weeks remaining higher in the triple combination including efavirenz group. Although the study was not designed to show a difference between the 2 triple combination arms it was subsequently amended to be so. The response rate was higher in efavirenz + lamivudine + zidovudine group compared to indinavir + lamivudine + zidovudine group. The response rate was also higher in the efavirenz + indinavir group compared to the triple combination control group including indinavir but the difference was not statistically significant.

The same pattern was seen when using the ultrasensitive HIV RNA assay.

The virologic failure rate was statistically significantly lower in the triple combination including efavirenz arm than in the triple arm including indinavir. The number of discontinuations due to adverse events was also lower, but was similar in both efavirenz-containing regimes (27 in each arm).

An analysis of the durability of response was performed, in which the duration of response was calculated from the time of first confirmed response (defined by a viral load less than 400 copies) to the time of treatment failure. No statistically significant differences between efavirenz + indinavir group and the control group were noted (p = 0.2463).

To further explore the relationship between baseline HIV RNA levels and plasma HIV RNA suppression at 48 weeks, results for the NC = F analysis were presented according to baseline HIV RNA less than or greater than or equal to 100,000 copies/ml. The results seemed to favour both triple combination arms for which the treatment results were not significantly affected by the baseline HIV RNA values whereas with the double combination a significantly better outcome was observed in patients with baseline HIV RNA lower than 100,000 copies/ml.

Study ACTG 364

The primary statistical comparisons for efficacy were based on efavirenz + nelfinavir + NRTIs versus nelfinavir + NRTIs. In this study, a cut-off of 500 copies/ml was used as the limit of detection. Interim analysis at 16 weeks showed a trend towards better results in the efavirenz-containing regimen. Patient discontinuation rate at 16 weeks was low and accounted respectively for 1 in nelfinavir + NRTIs group, 0 in efavirenz + NRTIs group and 5 in efavirenz + NRTIs + nelfinavir.

Further results at 24 weeks were provided and demonstrated that efavirenz in combination with 1 PI and 2 NRTIs in NRTIs-experienced patients was superior to the standard regimen PI + 2 NRTIs in terms of viral response. Unlike the other two triple therapy arms, the mean CD4 change from baseline was not statistically significant at 24 weeks from the baseline values.

The final results at 48 weeks have been later submitted and are presented in the table below:

Percentage of patients with plasma viral loads below the limit of detection at 48 weeks and change from baseline CD4 cell counts (cells/mm^3)

	Method of analysis	**Nelfinavir + NRTIs n = 66**	**Efavirenz + NRTIs n = 65**	**Efavirenz + NRTIs + nelfinavir n = 65**
Viral load below 500 copies per ml	ITT: NC=F	30.2 % # (45.3 %* #)	58.1 % (60.3 %)	70.3 % (78.0 %)
Change from baseline CD4 cell counts (cells/mm^3)	ITT: LOCF	93.8 (69.9)	113.8 (81.3)	107.4 (45.8)

** Statistical superiority demonstrated for efavirenz + NRTIs over nelfinavir + NRTIs*
 # Statistical superiority demonstrated for efavirenz + NRTIs + nelfinavir over nelfinavir + NRTIs

The response rate was statistically significantly higher in nelfinavir + efavirenz group compared to nelfinavir group for all treatment weeks (except week 16).

No statistically significant changes were observed between treatment groups with respect to CD4 cell counts. Statistically significant changes from baseline have however been observed across all treatment groups.

An analysis of the durability of response showed that both efavirenz + nelfinavir and efavirenz treatment groups had a significant longer time to treatment failure than the nelfinavir group.

Study DMP 266-020

In this study, 92 patients were included in each group and the most common prior NRTIs were ZDV and lamivudine. Patients were allowed to continue on their regimen of NRTIs or change to new NRTIs at the onset of the study and at the discretion of the physician. Patients were on a wide variety of single, double and triple combination NRTIs in addition to efavirenz and indinavir. An interim analysis was performed at 24 weeks. The results showed that a statistically significant difference with respect to the primary endpoint (percentage of patients with plasma levels of viral load < 400 copies/ml) in favour of efavirenz groups with the LOCF analysis. In the NC = F analysis the difference was however not statistically significant although there was a trend to better results**.** It was

shown that 63.7 % versus 52.2 % of patients (ITT: NC = F) receiving the quadruple regimen and standard regimen respectively had achieved viral suppression < 400 copies/ml. This corresponded to 54.3 % versus 35.6 % respectively who had achieved viral suppression < 50 copies/ml ($p < 0.05$).

Final results at 24 weeks obtained from 327 patients have been subsequently submitted. Greater percentage of patients in the efavirenz group had plasma HIV RNA levels < 400 copies/ml compared with the control group (59.6 % versus 50.9 % respectively) but this difference was not statistically significant. With respect to CD4 cell counts, significant mean increases from baseline were observed within both treatment groups at all point and at 24 weeks a significant difference in favour of the efavirenz group was noted (LOCF: 104 cells/ml versus 77 cells/ml respectively).

Supportive data

The interim reports for 5 supportive studies were provided. In one of the studies, results demonstrated the high efficacy of efavirenz + PI (nelfinavir), which further corroborated the results obtained in study 006. In another study, the efficacy and safety of a 2 doses regimen of indinavir were compared to a 3 doses regimen in combination with efavirenz bid and once daily. The data however were too limited to recommend a twice daily dosage regimen for efavirenz. The efficacy and safety of bedtime dosing were also evaluated in patients administered efavirenz in combination with indinavir. Although the number of patients dosed during daytime was too small to allow statistical analysis, a trend towards the increase in the most relevant adverse events was observed in this group, which might be in favour of a bedtime dosing.

The efficacy, safety and tolerability of efavirenz in patients with advanced HIV disease have not been evaluated. An adequate statement has therefore been included into the SPC to reflect this lack of data. Similarly although cross-resistance between efavirenz and PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based triple combination therapy after failure of efavirenz containing regimens.

Other studies to evaluate the efficacy and safety of efavirenz when used as part of combination therapies with other antiretroviral agents are ongoing. One of these studies is an ongoing open-label, one arm, non-randomised study in 60 patients taking efavirenz 600 mg QD + ritonavir 500 mg bid. Enrolment in this study has however been stopped after 33 patients have entered because of issues related to the lack of availability of ritonavir hard capsules. Only limited data is therefore available for a small subset of patients that have reached week 16. Observed data show that based on 17 patients approximately 35 % of patients have plasma HIV RNA < 400 copies/ml at week 4. At week 12 based on 6 patients 85 % of patients have plasma HIV RNA < 400 copies/ml. Mean CD4 cells levels increase by approximately 160 cells by week 12.

Study in children

Study ACTG 382

Details of the study protocol are desribed in the section: “pharmacokinetics”.
The primary efficacy measures were the percentage of patients with plasma HIV-RNA levels <400 copies/mL quantified by the Amplicor assay and the percentage of patients with plasma HIV-RNA levels <50 copies/mL quantified by the ultrasensitive assay. Secondary measures of efficacy included time to treatment failure (TTF), duration of response, change from baseline in $\log_{10}$ transformed plasma HIV-RNA levels, and mean change from baseline in CD4 count.

These results are summarised in the following table:

Measure	Cohort I (48 weeks)	Cohort II (32 weeks)
HIV-RNA < 400 copies/mL		
NC=F	34/57 (59.6%) (46.9, 72.4)	12/18 (66.7%) (44.9, 88.4)
LOCF	40/57 (70.2%) (58.3, 82.1)	13/18 (72.2%) (51.5, 92.9)
HIV-RNA < 50 copies/mL		
NC=F	30/57 (52.6%) (39.7, 65.6)	3/10 (30.0%) (1.6, 58.4)
LOCF	31/57 (54.4%) (41.5, 67.3)	12/18 (66.7%) (44.9, 88.4)
Mean change from baseline in log10 transformed HIV-RNA levels		
LOCF	-1.07 (±0.11)	-1.71 (±0.15)
Mean change from baseline in CD4		
LOCF	63 (±35)	378 (±69)

Response rates (<400 copies/mL) at 32 weeks for children under 5 years of age were 62.5% as compared to 70.0% in children aged 5 to 8 years. When using the Ultrasensitive assay (<50 copies/ml), response rates (NC=F) were 40% and 20%, respectively, for the <5 and 5 to 8 years age groups, respectively, although rates are affected by missing HIV-RNA data. At 20 weeks, when more data are available, response rates are 66.7% (12/18) and 70.6% (12/17).

These results were not significantly different from those generally found for the adult population, especially when the results of DMP 266-024, the only open-label, non-comparative study that evaluated the efficacy of the nelfinavir + efavirenz combination in adults

Clinical safety

Patient exposure

The safety database for efavirenz consisted of data collected from healthy subjects (n = 222, all doses and regimens included) and HIV infected patients in about 30 Phase I, II and III studies. Efavirenz has been studied in combination with NRTIs, predominantly zidovudine and lamivudine, with protease inhibitors (mostly with indinavir) and both with NRTIs and PIs. A total of 2,215 patients were exposed to efavirenz at any doses across all studies of which 855 for at least 24 weeks. Over 2000 patients received the intended dose for marketing of 600 mg daily, 764 for at least 24 weeks. Safety data from controlled clinical studies (phase II/III) included 413 patients who received 600 mg efavirenz and 297 patients who were treated with control regimens. Data from 381 unaffected volunteers who received efavirenz were also submitted. Additional safety information from patients exposed to efavirenz up to 48 weeks was provided.

Overall 43 of the 746 efavirenz treated patients (5.8 %) discontinued from clinical studies due to an adverse event compared to 8.5 % in the non-efavirenz treated patients. The most common adverse events which led to discontinuation in the efavirenz treated group were gastrointestinal symptoms, nervous system symptoms, rash, headache, fatigue and increased LFTs (mostly in patients with hepatitis B and C).

Adverse events

The most common adverse events observed in more than 10 % of the patients (n = 413) receiving 600 mg efavirenz, included nausea (29.1 %), dizziness (26.6 %), headache (23.5 %), diarrhoea (23.5 %), fatigue, vomiting, maculo-papular rash (14.8 %), insomnia (13.3 %), and impaired concentration (11.4 %). Statistically higher adverse event rates in efavirenz-treated compared with control-treated patients (n = 297) were noted for dizziness, maculopapular rash, concentration impaired, depression, nervousness, dreaming abnormal and euphoria. Although frequently reported, these adverse events were rarely of serious nature and only occasionally led to discontinuation of the treatment. They were generally of early onset and tended to attenuate or disappear with time even under treatment. Data from study DMP 266-006 up to 48 weeks indicated that adverse events might still develop after the 24 week of treatment with efavirenz. The most concerning adverse events associated with efavirenz therapy were nervous system symptoms and skin rash.

The safety profile of different doses of efavirenz was similar in terms of the incidence of new-onset adverse events, although significantly higher frequencies of dizziness (23.6 % with 600 mg versus 16.2 % with 200 mg) vomiting (13.0 % with 600 mg versus 4.8% with 200 mg) and somnolence (7.1 % with 600 mg versus 1.0 % with 200 mg) were noted with higher doses. However the more favourable pharmacokinetic profile demonstrated for this dose which was associated with increased exposure and higher mean trough levels, justified its choice as the proposed dose in clinical use.

An updated safety analysis from the controlled clinical studies was later presented on 1,643 patients of who 1,008 received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs. The incidence of undesirable effects already identified at the time of the CPMP opinion have been subsequently updated in the Summary of Product Characteristics according to the availability of the new data.

Rash

In clinical studies, 28 % of patients treated with 600 mg of efavirenz experienced skin rash compared with 18 % of patients treated in control groups. The updated safety information, available during the post-authorisation phase showed similar frequencies of 26 % and 17 % respectively. Skin rash was considered treatment related in 18 % of patients treated with efavirenz. Severe rash occurred in less than 1 % of patients treated with efavirenz and 1.7 % discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson Syndrome was approximately 0.1%. No cases of toxic epidermal necrolysis have been reported.

Rashes were usually mild-to-moderate severity not dose related, with a median time to onset of 11 days (range 0,171 days) and duration of two weeks (range 1 to > 174 days). The rashes were described as urticaria, maculopapular, erythematus or pruritic and rarely associated with fever. Palliative therapy with antihistamines and/or corticosteroids was often initiated, but the benefit of these therapies has not been established in controlled studies. In most patients rash resolved with continuing therapy with efavirenz within one month. In thirteen patients efavirenz was reinitiated after interrupting therapy because of rash and no recurrence was observed.

Limited data from 19 patients enrolled in a named patient programme who due to intolerance to nevirapine manifested by rash were treated with efavirenz were submitted. Of these, 9 developed mild to moderate rash while on efavirenz and only 2 discontinued as a result of rash.

Nervous system symptoms

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration, and abnormal dreaming were frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. In controlled clinical studies where 600 mg efavirenz was administered with other antiretroviral agents, 22.8 % of patients experienced nervous system symptoms of moderate to severe intensity compared to 10.1 % of patients receiving control regimens. In 2.9 % of patients these symptoms were of Grade 3 in the efavirenz group compared with 1.3 % in control group. In clinical studies 2.7 % of patients discontinued efavirenz therapy because of nervous system symptoms. Nervous system symptoms usually begin during the first or second day of therapy and generally resolved after the first 2-4 weeks. In uninfected volunteers in multiple dosed studies with efavirenz monotherapy, reported adverse events included euphoria (8.7 %), abnormal dreaming (4.6 %). The median time to onset of euphoria was 1 hour post dose (range 0.03 – 3.9 hours) with a median duration of 3 hours. The mechanism behind the nervous system symptoms associated with efavirenz treatment is unknown. In the controlled study DMP 266-006, there was a higher risk for depression and nervousness in the efavirenz + indinavir group versus indinavir + zidovudine + lamivudine which suggests an iatrogenic effect to efavirenz. As already indicated, bedtime dosing appeared to improve the tolerability of efavirenz, although the number of patients in the study is too small to perform statistical analysis. The applicant has committed to investigate the effects of lorazepam on efavirenz-associated CNS effects. During the post-marketing surveillance, it appeared that these nervous system symptoms were usually encountered during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks.

In addition there were reports (around 1-2 per 1,000 patients treated with efavirenz) of psychosis-like reactions, such as delusions and inappropriate behaviour in patients treated with efavirenz especially in patients with an history of mental illness or substance abuse. There is currently too limited data to

define the potential risk factors associated with these effects. After efavirenz discontinuation, the time to nervous system symptoms resolution accounted for a median of 1 day which contrasted with the median of 12.5 days reported in patients who continued treatment with efavirenz.

An analysis of suicide (completed, attempted or suicide ideation) was also performed based on the safety database and on the spontaneous adverse event reporting either from expanded access programmes or post-marketing surveillance. Based on this analysis, an appropriate statement has been introduced into the SPC to recommend the use of efavirenz with caution in patients with a history of pre-existing psychiatric disorders or drug abuse. The relationship between efavirenz and completed suicide and suicide attempt/ideation cannot be ruled out; this issue requires to be clarified through a rigorous prospective study or a case control study.
The correlation between the occurrence of nervous system symptoms and plasma level of efavirenz is under investigation in order to provide clear recommendation to prescribers on how to handle efavirenz when concentrations are likely to increase (e.g. concomitant food-intake).

During the post-authorisation phase, occurrence of psychiatric symptoms is closely monitored. There have also been reports of severe depression, death by suicide, delusions and psychosis-like behaviour.

In the 874 efavirenz treated patients in controlled trials, pancreatitis was not reported. In the expanded access programme, 47 cases among 17,000 patients exposed (< 0.3 %) were reported but no cases were clearly related to efavirenz. An appropriate statement has however been included into the SPC.

Cases of neurosis, paranoid reactions, convulsions, blurred visions, pruritus, abdominal pain, gynaecomastia and hepatic failure have been reported in the updated safety information, available during the post-authorisation phase.

Serious adverse events and deaths

Approximately 80 of the 2,215 (4 %) efavirenz-treated patients reported a serious adverse event. Of these 34 were considered possibly related to efavirenz. Most of the serious adverse events reported related to nervous system disorders (one seizure), liver biliary system disorders (increased ALT, AST, γ-GT, ALP) and haematology disorders. One patient had a grade 4 increase in CK. Three cases of grade 4 rash were also reported.

None of the five deaths that occurred in patients receiving efavirenz was related to the product.

Laboratory findings

Elevations of γ-GT were common in the efavirenz-treated group, which may reflect an enzymatic induction. The incidence of AST and ALT abnormalities did not differ between efavirenz-treated patients without a history of hepatitis and control patients. In 53 patients treated with 600 mg of efavirenz who were seropositive for hepatitis B and/or C, 6 % developed AST levels and 13 % developed ALT levels greater than 5 upper limit of normal (ULN) versus 5 % and 2 % respectively in control group (n = 41). Elevations of γ-GT to greater than five times ULN were observed in 4 % of all patients treated with 600 mg of efavirenz and in 11 % of patients seropositive for hepatitis B or C versus in the control group. The monitoring of liver enzymes in patients with hepatitis B or C is therefore warranted as indicated in the SPC. Updated data provided by the applicant showed that over 35,000 patients receiving efavirenz, including 17,000 patients in the expanded access programme, treatment related hepatic failure was not reported.

An increased triglyceride and cholesterol and glucose levels were reported with efavirenz treatment as well as a new onset of insulin-dependant diabetes mellitus. The protocol of study DMP 266-006 was amended to include measurements of cholesterol, triglycerides in newly enrolled patients at baseline and at each visit. Elevation of total cholesterol was greatest in the efavirenz + indinavir group.

Preliminary results suggested that efavirenz appeared associated with increases in blood cholesterol and this increase might consist mostly of HDL cholesterol moiety. Further results showed that increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 % respectively were observed in patients treated with efavirenz + zidovudine + lamivudine and of approximately 40 % and

35 % in patients treated with efavirenz + indinavir. The effects of efavirenz on triglycerides and LDL are not well defined. The clinical significance of these findings is currently unknown.

A statistically significant difference in the incidence of increases in serum amylase levels was also observed between efavirenz-treated and control groups and was therefore introduced in the SPC.

Safety profile of efavirenz in combination

Efavirenz was studied in combination with other antiretroviral agents. The tolerability of the different combinations evaluated was acceptable. No new adverse events or changes in expected frequency or severity of adverse events were observed in patients receiving PIs. Efavirenz in combination with ritonavir (500 mg q 12h) administered in healthy volunteers or in infected patients (maximum 600mg ritonavir dose) was not well tolerated and was associated with higher frequency of adverse events (e.g. dizziness, nausea) and laboratory abnormalities (elevated liver enzymes) as already indicated in the clinical efficacy part.

Although nephrotoxicity was observed in rats treated with efavirenz, the clinical studies in humans have not indicated any signs of nephrotoxicity.

Experience in Post-Authorisation surveillance

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 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.

Safety in special populations

Gender and race
The patients included in the efavirenz safety database are representative of the population affected by HIV disease (83 % male, 58 % White, 19 % Black, 10 % intravenous drug abusers, 65 % homosexual/bisexual in patients receiving 600 mg efavirenz in controlled studies). No significant difference in terms of adverse events has been reported according to the age, racial group and other demographic parameters.

Elderly

Because of the demographic of the disease and the enrolment criteria in the clinical studies, the safety profile of efavirenz in adults above 65 years old has not been established.

Paediatric

Safety of efavirenz in children was assessed in the ACTG 382 study. The type of adverse events reported in children taking the capsule formulation, was similar to the ones in adults. The most important effect reported was rash reported with an incidence higher compared with adults (35 % instead of 28 % in adults). Among them two children had Grade 3 rash. Five patients discontinued therapy because of rash, which represented a higher discontinuation rate (9 %) compared to adults (1.7 %). The most common adverse events reported were diarrhoea (26 %), fever and cough.

Nervous system symptoms were only reported occasionally (5 %). At the 48 week time point, rash was reported in 23/57 patients (40 %) including 2/57 patients of Grade 3 (3.5 %) and 2/57 patients (3.5 %) of Grade 4. The median time to onset for rash was 9 days (range 6-247 days) and the median duration was 4.5 days. Severe rash was shown to be manageable by discontinuation of the treatment.

The additional data submitted at 48 weeks did not reveal any new adverse events but updated the incidences as reflected in the SPC. They confirmed a trend towards a greater incidence and severity of skin-related adverse events in children than in adults.

Safety data with the liquid formulation C in HIV-infected children is derived only from the 19 patients included in Cohort II of study ACTG 382. Overall, and despite the small number of patients, the most relevant safety finding is the reduction in the incidence of rash in patients treated with the liquid formulation as compared to the capsules, which must be better evaluated in a significant number of patients.

5. Overall Conclusions and benefit/risk assessment

The quality of this product was considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the uniform clinical performance of the product were investigated and were controlled in a satisfactory way.

Taking into consideration the therapeutic indication of efavirenz, the pharmacological and toxicological profile was satisfactory defined although there were some concerns related to the efavirenz-mediated multifocal biliary fibrosis and centrilobular hepatocellular hypertrophy which needed further clarifications. Due to the suspicion of embryotoxicity with efavirenz in rats and the evident teratologic effects in cynomolgus monkey, efavirenz should not be given in pregnant women, as indicated in the SPC. Carcinogenicity studies of efavirenz were carried out on monkeys, rats and mice. The results showed an increased incidence of hepatic and pulmonary tumors in female mice, but not in male mice. The mechanism of tumor formation and the potential relevance for humans are not known.

In this therapeutic area where all the agents have to date relatively narrow therapeutic windows, it is justified to administer in combination, an agent at its maximally tolerated dose. The maximally tolerated dose of efavirenz has not been determined. The dose of 600 mg once daily was however the more favourable pharmacokinetic profile and was associated with increased exposure and higher mean trough levels, which justified its choice as the proposed dose in clinical use. This dose was also associated with an acceptable safety profile.

The efficacy data including preliminary data up to 48 weeks showed that efavirenz at the dose of 600 mg, either in combination with a PI or 2 NRTIs was a valuable therapeutic alternative for HIV infected patients. Efavirenz in combination showed higher response rates than standard PI/NRTI treatment regimens in two independent studies. In study DMP 266-006, data up to 48 weeks showed that efavirenz in combination with zidovudine and lamivudine was at least as effective to the combination indinavir/lamivudine/zidovudine in NRTIs-experienced in terms of percentage of patients with viral load below the limit of detection. In study ACTG 364, efavirenz in combination with nelfinavir plus NRTIs was superior to the standard regimen nelfinavir + NRTIs in NRTIs-experienced patients. An analysis of durability of response showed that both efavirenz + nelfinavir and efavirenz treatment groups had a significant longer time to treatment failure than the nelfinavir group. The efficacy of efavirenz in children was based on the extrapolation of data from adults and on the data from study ACTG 382. A suitable paediatric formulation has been developed. However, a concern is raised with regard to the compliance with the oral solution formulation that was applied for. This reduced compliance, may be related either to poor palatability of the formulation and/or with dosing accuracy from the care providers. To address this issue, a revised treatment nomogram for the formulation has been adopted. This may help to overcome the problem of underexposure in children younger than 5 years. However, for the time being, the usefulness of the oral solution, is not evident in the data from children over 3 years who are able to swallow the capsules. Hence, the restriction to reserve oral efavirenz solution only to those who are unable to swallow the capsules or film-coated tablets.

The efficacy, safety and tolerability of efavirenz in patients with advanced HIV disease (namely < 50 cells/mm^3) have not been evaluated. An adequate statement has therefore been included into the SPC to reflect this lack of data. Similarly although cross-resistance between efavirenz and PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based triple combination therapy after failure of efavirenz containing regimens.

At the time of the Marketing Authorisation, over 2,000 patients received the intended dose for marketing of 600 mg daily, 764 for at least 24 weeks. The safety of efavirenz in the clinical setting was mainly related with the nervous system, with the occurrence of rash and with the development of changes in liver function tests. Although frequently observed, the adverse events were rarely of serious nature and only occasionally led to discontinuation of the treatment. These adverse events were considerably well characterised in terms of the time of appearance and duration, and discontinuation of treatment was not mandatory in most of the events. They were generally of early onset and tended to attenuate or disappear with time even under treatment..

The limited safety data in children treated with efavirenz capsules indicated that the type and the frequency of adverse events in children was generally similar to that in adult patients, with the exception of rash which was reported more frequently and was more often of higher grade. With reference to safety of the liquid formulation in children, the submitted data are scarce. Further evaluation, under appropriate dosing conditions (i.e., with the commercial formulation) in a significant number of paediatric patients is awaited.

Benefit/risk assessment

Concerns were raised during the CPMP discussion which pertained to the safety and efficacy of efavirenz in a paediatric population. During the oral presentation in front of the Committee, the applicant presented preliminary data from study ACTG 382 up to 48 weeks. The complete data set at 20 weeks showed the durability of the efficacy of efavirenz up to 20 weeks with more than 61 % (95 %: CI 48-74) of patients with plasma viral load below the limit of detection in the ITT-NC = F analysis. The CD4 cell counts at 20 weeks increased by 100 ± 37.5 cells/ mm^3 from baseline. The concern of safety in children was further addressed and further data were submitted to show that efavirenz is generally well tolerated and that rash is identifiable and manageable.

Based on the available data on quality, safety and efficacy and the subsequent discussion within the Committee, the CPMP considered by consensus that the benefit/risk profile of Sustiva for use in antiviral combination treatment in HIV infected adults and children over 3 years of age patients to be favourable and recommended a positive opinion on the granting of the marketing authorisation for Sustiva 50, 100 and 200 mg hard capsules for the following indication: “Sustiva is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children of 3 years of age and older”. The film-coated tablets 300mg and 600mg received the identical indication, whilst the oral solution is reserved to those unable to swallow the solid formulations.

The final efficacy and safety data up to 48 weeks from the main studies which were provided after the CPMP opinion was granted did not affect the benefit/risk of Sustiva but led to adequate changes to the product information.