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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Viracept

nelfinavir

Procedure No.: EMEA/H/C/000164/II/0119

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000164/II/0119

Name:	Viracept
Common name:	nelfinavir
Indication summary (as last approved):	Treatment of HIV-1 infections
Marketing authorisation holder:	Roche Registration Ltd.

1. Scientific discussion

1.1. Introduction

Viracept contains the active substance nelfinavir, an inhibitor of Human Immunodeficiency Virus (HIV) protease. Nelfinavir belongs to the pharmaco-therapeutic group of Protease Inhibitors.

Nelfinavir is indicated in antiretroviral combination treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children of 3 years of age and older. In protease inhibitor (PI) experienced patients the choice of nelfinavir should be based on individual viral resistance testing and treatment history. Both Viracept oral powder 50 mg/g and Viracept film-coated tablets 250 mg are currently authorised.

Nelfinavir was first approved for clinical use in the EU in January 1998. At the time of approval there were very limited pharmacokinetic (PK) data available from a specific study in HIV-infected children aged > 2 years that supported a dosage regimen of 20-30 mg/kg body weight administered three times daily (TID) either as tablets or using the oral powder. Administration was to be with a meal or light snack.

After initial approval, data from additional PK studies in HIV-infected children showed lower plasma exposure compared to that achieved in adults with the same dose regimen, which raised a concern that 20-30 mg/kg TID could result in virological failure in children. Furthermore, studies in children ranging in age from newborns to 18 years showed significant inter-subject variability in nelfinavir pharmacokinetics. This may reflect a combination of factors including not taking nelfinavir with adequate amounts of food, not taking the entire dose (especially in very young children) and either increased clearance or poor absorption.

Since 1998 the accumulated experience has led to recommendations for either twice daily or thrice daily dosing for children aged from 13 years and adults as well as for children aged from 3 to 13 years. In children aged 3 to 13 years the recommended starting dose ranges are 25-30 mg/kg TID or 50-55 mg/kg BID in the currently approved SmPC.

The MAH has submitted a variation in order to change the current dose recommendations for children aged 3-13 years when using either the Viracept oral powder 50 mg/g or Viracept film coated tablet 250 mg based on four studies performed in children. The MAH has proposed to increase the TID dosing regimen from 25 to 30 mg/kg to 25 to 35 mg/kg body weight on grounds that it is less likely to lead to inadequate plasma exposure.

In summary, the variation concerns a change to the starting dose when administering Viracept in three divided doses daily (TID) to children aged 3-13 years. There are no changes to actual dosing recommendations for older subjects or for children aged 3-13 years when administering Viracept in two divided doses daily (BID).

However, the MAH has also proposed to add recommendations into the tables for TID dosing for tablets for children of < 18 kg body weight and include advice on dissolving the tablets to facilitate their use as an alternative to the oral powder.

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

1.2. Clinical aspects

Revision of the recommended TID Dosing Regimen

Clinical studies

The MAH has submitted an overview of the data collected from four studies conducted in children that have assessed plasma exposures against a target adult AUC24 of 43-53 mg*hr/L :

- *Agouron study 524* – children <3 months to 13 years, N = 65
- *Agouron study 556* – children 3 months to 12 years, N = 141
- *PACTG377* - children 3 months to 13 years, N = 62

Including a PK *sub-study PACTG725* – children 3 to 11 years, N = 11

- *PENTA-7* – children <3 months, N = 20

These studies are further described below and a summary is provided in table 1.

Table 1: Summary of studies provided by the MAH

Protocol No. [ref]	Dosing Regimen[1]	N	Age	AUC_{24} (mg.hr/L) (n with PK data)
AG1343-524 **[8333]**	20 (19-28) mg/kg TID	65	< 3 months - 13 years	56.1 ± 29.8[b] (n = 14)
AG1343-556* **[8335]**	25-35 mg/kg TID	141	2 – 12 years	38 (9-121)[d] (n = 86)
PACTG-377 **[8425]** , **[10001]**	30 mg/kg TID[a]	52	3 months – 7 years 7 years – 16 years	34.2 (20.7 – 61.5)[c] (n = 9) 89.4 (24.8 – 135.3)[c] (n = 11)
Substudy PACTG-725 **[8426]**	55 (48-60) mg/kg BID[a]	11	3 months – 13 years	101.8 ± 56.1[b] (n = 6)
PENTA 7 **[8427]**	40 (34-43) mg/kg TID switched to 75 (55-83) mg/kg BID	20	0.9 – 4.7 months	33.8 ± 8.9[b] (n = 4) 37.2 ± 19.2[b] (n = 12)

[1] Protocol specified dose (actual dose range where available)
* PK data from Study AG1343-556 were more variable than data from other studies conducted in the paediatric population and of limited value
[a] Number of subjects treated with NFV in absence of NVP.
[b] Arithmetic mean ± SD
[c] Median (range)
[d] Mean (95% CI)
Targeted adult exposure of AUC_{24} of 44-53 mg*hr/L

As shown in table 1, these studies used a range of nelfinavir doses and schedules to identify regimens that provided plasma exposures associated with efficacy in adults (AUC24 of 44 mg*h/L for the adult TID dose and 53 mg*h/L for the adult BID dose).

Agouron study 524 was an open-label multicentre study conducted in two parts. The first segment evaluated the safety, tolerability and PK of single dose nelfinavir to select a likely dose. The second segment involved dosing at TID over 6 weeks with the dose selected during the first segment. There was an option to continue with TID dosing for up to 22 months.

All patients received nelfinavir in combination with nucleoside reverse transcriptase inhibitor (NRTIs). A target plasma concentration of 50%-200% of the median exposure in adults after a 750 mg single dose was used to identify paediatric doses by age sub-group.

The mean age of the 64 children enrolled was 4.3 years with 16 aged 7-13 years, 23 aged 2-<7 years and 25 aged <2 years. The mean baseline HIV RNA value was 4.6 log10 cfu/ml and the mean CD4% was 23.8%. After 11 months of the extension study the mean CD4% was 36.1% and the mean HIV RNA was 3.45 log10 cfu/ml. Of those subjects remaining in the study at this point, 20% (13/32) had <400 copies/mL.

Agouron study 556 was a Phase III, randomised, double-blind study that compared nelfinavir (25-35 mg/kg TID) with placebo each co-administered with zidovudine (ZDV) and didanosine (ddI) in 141 HIV-positive children who had received minimal prior antiretroviral therapy (ART). The mean age of the children was 3.9 years and 94 (67%) were aged 2-12 years while 47 (33%) were aged <2 years. The mean baseline HIV RNA was 5.0 and 5.1 log10 cfu/ml in the two treatment groups and the mean CD4% was 20%.

The percentage with HIV RNA <400 at 48 weeks in children aged ≥ 2 years was 26% in the nelfinavir group and 2% in the placebo group (p=0.0008). In those aged <2 years only 1/27 placebo and 2/20 nelfinavir group subjects maintained an undetectable HIV RNA level at 48 weeks. In both treatment groups, CD4% and absolute counts increased from baseline and the Week 48 mean CD4% for nelfinavir and placebo subjects still on study was 29%.

PACTG 377 was an open-label study that randomised 181 HIV treatment-experienced children to one of:

- d4T+NVP+RTV
- d4T+3TC+NFV
- d4T+NVP+NFV or
- d4T+3TC+NVP+NFV

d4T=2'-3'-didehydro-2'-3'-dideoxythymidine, stavudine; NVP=nevirapine; RTv=ritonavir; 3TC=2',3'-dideoxy-3'-thiacytidine, lamivudine; NFV=nelfinavir

In each case NFV was given at 30 mg/kg TID. The median age of subjects was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log 10 cfu/ml and the median CD4 cell count was 690 cells/mm3. The MAH also provided the publication from this study.

Sub study PACTG 725 evaluated d4T+3TC+NFV with NFV given at 55 mg/kg BID to 11 subjects of <30 kg. The median age was 7.8 years, the median CD4 cell count was 710 cells/mm^3 and median HIV RNA was 4.4 log10 cfu/ml.

The proportions with detectable viral load at baseline that had HIV RNA <400 copies/mL at 48 weeks were 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between those who received NFV at BID or TID schedules.

PENTA 7 was an open-label study that evaluated a NFV+d4T+ddI regimen in 20 HIV-infected infants aged < 12 weeks. The mean age was 2.6 months (range 0.9 to 4.7 months), median HIV RNA was 5.51 log10 cfu/ml and median CD4% was 33%. By week 48, 37% had <400 copies/mL and 21% had <50 copies/mL. The median change from baseline in absolute CD4 count at week 48 was 170 cells/mm^3 and the median change in CD4% was 1%.

Safety data obtained in the studies indicated that the doses were reasonably well tolerated across the age range. While adverse events (AEs) were common, relatively few were considered drug related (with the exception of diarrhoea), severe in intensity or required discontinuation of study drug. As in adults the most common AE associated with NFV was diarrhoea, which was reported in 39 - 47% of subjects. Neutropenia/leucopenia was the most commonly observed significant laboratory abnormality and was of Grade 3 or 4 in 14 - 16% of subjects. However, discontinuations due to laboratory abnormalities were rare.

The MAH concluded that not all of these paediatric studies identified doses that achieved the target plasma exposures and considerable variability in the PK data was noted. Because of this marked variability, dose selection required evaluating the available PK data in conjunction with the clinical (efficacy and safety) data. The MAH concluded that there were clinical concerns that the currently

approved TID dose results in frequent virological failure and that the data from children aged 2 to 13 years (in Agouron study 524, Agouron study 556 and PACTG 377) showed that 25-35 mg/kg TID provided nelfinavir exposure associated with clinical evidence of activity over 48 weeks of dosing. Therefore, the MAH proposed an increase in the TID dose for children aged 3 to 13 years to 25 to 35 mg/kg.

Literature review

As per request of the CHMP, the MAH further conducted a literature research to assess all relevant published data and experience accumulated in children.

The review of published literature was performed by searching for the terms *nelfinavir*, *paediatric*, *children* and *HIV* in the U.S. National Library of Medicine, NIH Pubmed database. In addition, references from HIV treatment guidelines from Europe and the U.S. were reviewed. A number of published studies were identified that are not relevant to this review because the focus is on children ≥ 3 years of age.

The initial study of Viracept (study AG1343-524) in children evaluated doses of 20-30 mg/kg three times daily (TID) administered as tablets or powder in HIV-infected children and exposed infants. This study enrolled 62 children aged from 3 months to 13 years and found that steady state nelfinavir exposures in children administered 20-30 mg/kg TID were comparable to those in adults taking 750 mg TID.

Table 2: Steady state pharmacokinetics of nelfinavir in children and in adults

	Median value (interquartile range)	
PK Parameter	**Pediatric 23 ± 3 mg/kg (n = 19)**	**Adult 750 mg (n = 41)**
AUC_8 (mg*h/L)	19 (13 – 30)	16 (13 – 30)
Cmax (mg/L)	3.8 (2.6 – 5.0)	2.9 (2.3 – 4.1)
Cmin (8 hr mg/L)	1.5 (0.7 – 2.8)	1.2 (0.9 – 1.6)

[Krogstad 1999] [8289]

In a study that evaluated nelfinavir 30 mg/kg TID combined with saquinavir soft gel capsule 33 mg/kg TID and NRTIs in 11 children aged 3 to 16 years there was no assessment of nelfinavir PK but there was increased exposure to saquinavir with no major safety issues[1]. A study that evaluated 23 HIV-infected children aged 0.3 to 16.9 years reported that 12 (52%) receiving nelfinavir had a sustained plasma HIV-1 RNA level decrease > 1.0 log10 from baseline. The authors noted that virological rebound after week 12 may have reflected insufficient doses of nelfinavir in some cases[2].

An observational cohort evaluated the long term safety and efficacy of PIs including nelfinavir (dosed as 30 mg/kg TID) taken between 1996 and 2003 in 133 HIV infected children in the Swiss Mother and Child HIV Cohort Trial. The mean age of 86 children taking nelfinavir was 7.7 years (0.1 – 16.9 years) and the the total duration of exposure was 235 patient-years[3]. Virological response at 48 weeks was

[1] Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children, Markus B. Funk, AIDS 1999, 13:1653–1658
[2] Long-Term Responses to Treatment Including Ritonavir or Nelfinavir in HIV-1-Infected Children, D. Nadal, Infection 2000; 28:287-296
[3] Long-Term Safety and Effectiveness of Ritonavir, Nelfinavir, and Lopinavir/Ritonavir in Antiretroviral-Experienced HIV-Infected Children, Christoph Rudin, Pediatr Infect Dis J 2008;27: 431–437

observed in 55% (33/60) receiving nelfinavir, in 66% taking RTV-based regimens and in 69% receiving lopinavir/ritonavir (LPV/RTV). While the study was ongoing, the nelfinavir dose was increased to 30–40 mg/kg TID.

The ANRS1248/1277 cohort compared the responses to nelfinavir (administered to 60 children at doses of 90 mg/kg TID or BID) and to efavirenz in 16 children in Côte d'Ivoire. Suppression of detectable HIV-1 RNA viral load was achieved in 40% (95% CI, 27.0–54.1), 46.5% (95% CI, 31.2–62.3) and 45% (95% CI, 23.1–68.5) of children, respectively, at 30, 36 and 42 months of follow-up.

A prospective cohort evaluated long-term nelfinavir administered at 30 mg/kg TID or 45 mg/kg twice daily (BID) in 39 treatment-naïve or experienced HIV-infected children[4]. Children of median age 4.7 years (range: 1.1 to 8.8 years) took nelfinavir for a median duration of 185 weeks (IQR: 69.5–264.9 weeks). Study medications were discontinued in 26 (69%) children due to virological failure, poor palatability of oral powder, simplification of therapy or AEs.

A small study that compared BID to TID dosing evaluated the virological response and trough concentrations of nelfinavir 20 – 30 mg/kg TID in 15 children (mean 7.6 years of age) vertically infected with HIV-1. The geometric mean trough concentration of the TID regimen group was 1.55 mg/L (range 0.13–5.22 mg/L). However, peak and trough concentrations did not correlate with total daily dose, mg/kg dose, age, weight, previous PI use or CD4+ counts. At Week 24 there was a mean viral load reduction of 2.1 (+1.2 SD) log10 copies/mL in the TID regimen group. On univariate analysis, the decrease in the virus load at 24 weeks of treatment was not correlated with trough concentration of nelfinavir but there was a trend toward a decreased viral load in patients with higher trough concentrations[5].

HIV-infected children (n=50) participated in an AUC-controlled study while taking nelfinavir 20 – 30 mg/kg TID (mean 24 mg/kg TID) plus efavirenz and NRTIs[6,7]. PK evaluations were performed at weeks 2, 6 and 56 and doses were adjusted to achieve AUC8 values ≥10 mg*h/L. The median age of children was 7 years (range 3-16 years) and mean body weight was 24 kg (range 13.4-98 kg). A relationship between AUC8 and C8 with virologic response was observed (Table 3). Dose adjustments to achieve at least AUC 10 mg*h/L reduced the risk of suboptimal exposure and achieved high rates of virological suppression. The mean week 2 CL/F was approximately 3.4-fold faster than in adults and increased by 62% over 56 weeks. The proportion of children who achieved target AUC values at week 56 was less than that at week 10 which may reflect changes in clearance. The study showed no difference in nelfinavir PK at week 56 between those who did and did not have a virological response.

[4] Long-term Experience With Combination Antiretroviral Therapy That Contains Nelfinavir for up to 7 Years in a Pediatric cohort, Henriëtte J. Scherpbier, Pediatrics 2006;117;e528-e536
[5] Pharmacokinetics and Pharmacodynamics of Nelfinavir Administered Twice or Thrice Daily to Human Immunodeficiency virus Type 1–Infected Children, G. Gatti, Clinical Infectious Diseases 2003; 36:1476–82
[6] Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1, Stuart E. Starr, N Engl J Med 1999;341:1874-81
[7] Pharmacokinetics and Pharmacodynamics of Efavirenz and Nelfinavir in HIV-infected Children Participating in an Area-under-the-curve Controlled Trial, CV Fletcher, Clin Pharmacol Ther. 2008 February; 83(2): 300–306.doi:10.1038/sj.clpt.6100282

Table 3: Comparison of nelfinavir PK characteristics with the proportion of children ≤ 400 versus > 400 copies/ml of HIV RNA

	AUC_8 (mg*h/L)	C_8 (mg/L)
Nelfinavir pharmacokinetics at week 2		
≤ 400 copies/mL	21.4	2.8
> 400 copies/mL	6.9	1.5
P value	0.01	0.038
Nelfinavir pharmacokinetics at week 6		
≤ 400 copies/mL	20.8	2.8
> 400 copies/mL	18.4	1.6
P value	0.36	0.11

AUC_8, area under the plasma concentration–time curve from time 0 to 8 h post-dose; C_8, measured concentration 8 h post-dose

A study that evaluated a small number of children increased the dose from 30 mg/kg TID to 40 and 45 mg/kg TID to achieve targeted dose adjusted AUCs of 13–20 mg/L[8]. In the Penta 5 study[9] nelfinavir was initially given at 20-30 mg/kg TID to children of median age 5.3 years but the dose was increased to at least 90-110 mg/kg daily. The children with a nelfinavir trough > 0.8 mg/L had better virological responses than those with lower troughs.[10]

In a study of 24 HIV-infected children aged from 5 months to 18 years, including 17 aged > 2 years[11], the median nelfinavir dose was 28 mg/kg q8h [IQR 26–31 mg/kg q8h] and the maximum absolute dose was 750 mg q8h. Of 22 children who completed 6 months treatment 16 (73%) had a response of HIV RNA <500 copies/ml. After stratification of the dose groups of 20 (n=5), 30 (n=14) and 40 (n=5) mg/kg nelfinavir q8h, the AUC0–8 showed a less than dose-proportional increase (median AUC0–8 of 8.7, 16.6 and 12.5 mg/l*h, respectively). However, there was significant variability in PK nelfinavir, particularly in the very young children. Virological response rates at 6 months in dose categories 20, 30 and 40 mg/kg TID were 50, 71 and 100%, respectively (P>0.1) but there was no significant relationship between nelfinavir plasma levels and efficacy. A virological response was observed in 80% of those with AUC0–8 <12.5 mg/l*h and in 71% of those with AUC0–8 >12.5 mg/l*h (P>0.1). Three of the five who took 750 mg TID had AUC0–8 values <12.5 mg/l*h. There may have been an effect of taking nelfinavir with food in older children and with formula in younger children.

The PACTG 377 study evaluated 140 children aged from 4 months to 17 years who received one of four regimens containing nelfinavir (30 mg/kg TID if < 30 kg and 27-33 mg/kg if > 30 kg; maximum TID dose 1250 mg/dose) [12,13,14]. HIV RNA < 400 copies/mL was observed in approximately 50% at 48

[8] Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants, Capparelli, Edmund V, Pediatr Infect Dis J. 2001 Aug;20(8):746-51
[9] Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial, Paediatric European Network for Treatment of AIDS (PENTA), Lancet 2002; 359: 733–40
[10] Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1 infected children, David M. Burger, J Pediatr 2004;145:403-5
[11] Pharmacokinetics of nelfinavir in children: influencing factors and dose implications, Alina S Bergshoeff, Antiviral Therapy, International Medical Press 2003; 8: 1359-6535
[12] Nelfinavir Pharmacokinetics in Stable Human Immunodeficiency Virus-Positive Children: Pediatric AIDS Clinical Trials Group Protocol 377, Leslie Carstensen Floren, Pediatrics 2003;112;e220-e227
[13] Combination Nucleoside Analog Reverse Transcriptase Inhibitor(s) Plus Nevirapine, Nelfinavir, or Ritonavir in Stable Antiretroviral Therapy-Experienced HIV-Infected Children: Week 24 Results of a Randomized Controlled Trial—PACTG 377, Andrew Wiznia, AIDS Research and human retroviruses Volume 16, Number 12, 2000, pp. 1113–1121
[14] Nucleoside-Analogue Reverse-Transcriptase Inhibitors Plus Nevirapine, Nelfinavir, or Ritonavir for Pretreated Children Infected with Human Immunodeficiency Virus Type 1, Paul Krogstad, Clinical Infectious Diseases 2002; 34:991–1001

weeks. A separate PK analysis of nelfinavir exposures was made for children >/< 25 kg, including a subset of > 30 kg who received 27-33 mg/kg TID (Table 4).

Table 4: Nelfinavir exposures in children < 25 kg and > 25 kg weight

	N	Median Age (Years)	Median Weight (kg)	Median AUC_{0-8} µg*hr/mL
Children < 25 kg	9	4.2 (0.6 – 7.0)	14.5 (8.8 – 21.6)	11.4
Children > 25 kg	11	9.8 (7.2 – 16.0)	33.7 (25.5 – 55.2)	29.8

[Floren 2003] [10023]

Median AUC was greater for children > 25 kg compared with those < 25 kg and some of the latter group had exposures less than the target AUC that correlated with virological response. However, AUCs in children < 25 kg varied from 6.9-20.5 µg*h/mL and the age range was from 0.6 to 7.0 years. Smaller children received the powder whereas those > 25 kg generally received tablets but all dosing was observed. The results suggested inadequate dosing in children < 25 kg.

The AG1343-556 study was designed to evaluate 25-35 mg/kg TID in 132 infants and children who were randomised (1:1) to Zidovudine/didanosine (ZDV/ddI) alone or combined with nelfinavir 250 mg tablets or 50mg/g powder (n=66) for 48 weeks, including 36 who were aged 3-12 years and received nelfinavir 25-35 mg/kg TID. A population PK approach was employed to examine the association of dose, PK and virological response using sparse PK sampling (pre-dose samples on weeks 4, 8, 12, 24 and 48 and one sample at 3 h post-dose at weeks 8 and 24).

The mean dose was 28.9 mg/kg (range 19.1-38.5 mg) and the mean AUC8 was 9.8 µg*h/mL (95% CI: 2.4-40.4 µg*h/mL). The significant variability in AUC was thought to possibly reflect the age range. Viral suppression was maintained more frequently when AUC8 was at least 12.5 µg*h/mL (54% response) vs. < 12.5 µg*h/mL (28% response). Doses required to achieve adequate exposures and virological response were closer to 35 mg/kg and most of the exposures above 12.5 µg*h/mL were associated with doses between 30 and 35 mg/kg as illustrated in Figures 1 and 2.

Figure 1: Association between Nelfinavir dose and AUC_8

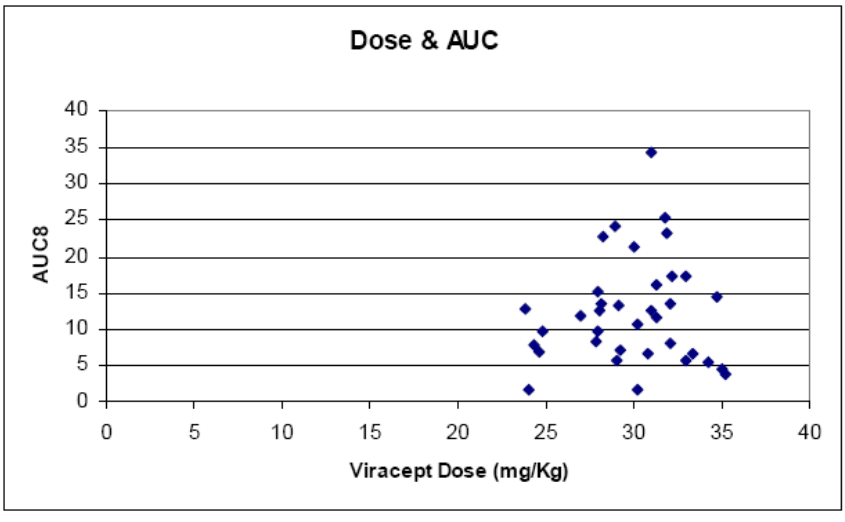
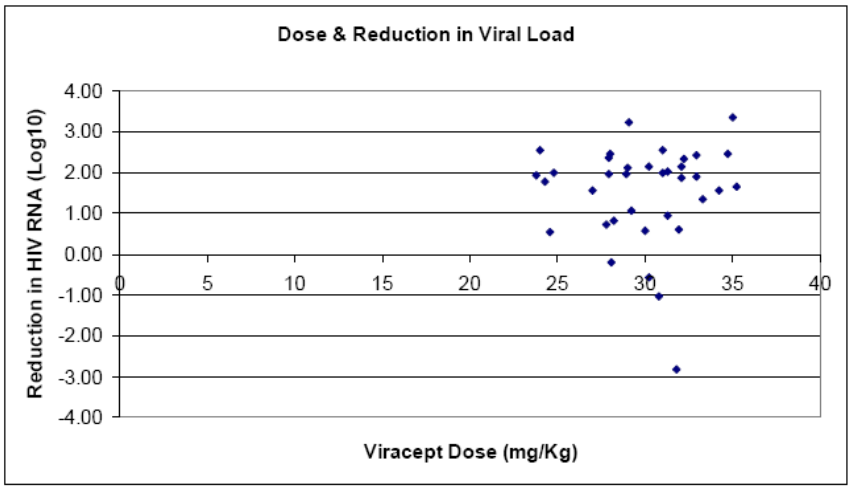


Figure 2: Association between nelfinavir dose and reduction in HIV



With increased doses, diarrhoea was reported as the most frequent AE. The AUC0–8 values observed in children > 25 kg in the PACTG 377 study (29.8 µg*h/mL) were greater than the exposures that were observed to correlate with acceptable virological responses in the AG1343-556 study (12.5 µg*h/mL). However, the frequency and severity of AEs in children taking 25-35 mg/kg was not significantly different than reported in the earlier study that evaluated 20-30 mg/kg TID (Table 5).

Table 5: Adverse events in children enrolled in AG1343-524 and AG1343-556 studies

	AG1343-524 [8289]	AG1343-556 [10026]
	20 – 30 mg/kg TID	25 – 35 mg/kg TID
N	64	66*
Number (%) of patients with treatment-emergent AEs	59 (92%)	61 (92%)
Number of treatment-emergent SAEs	17	25
Number (%) of patients with treatment-emergent SAEs	17(27%)	18 (27%)
Number (%) of patients who discontinued the study	29 (45%)	10 (15%)
Number (%) of patients who discontinued due to treatment-emergent AEs (all resulting in death)	1 (0)	2 (3)**
Number (%) of patients who died (all due to HIV-related events)	0	2 (3)
Diarrhea: number patients (%) reported	30 (47%)	26 (39%)

* Includes all children enrolled, age 0.3 – 12 years of age

** 2 deaths due to death from HIV-related events; one from meningococcemia and one from multi-organ failure resulting from Pneumocystis carinii pneumonia.

The most frequently reported AEs in AG1343-524 were rhinitis (61%), fever (48%), diarrhoea (47%), lymphadenopathy (38%), increased cough (33%), rash (31%), otitis media (31%) and vomiting (27%). In AG1343-556 the most frequently reported AEs were diarrhoea (39%), otitis media (32%), fever (29%), pharyngitis (29%), lung disorder (26%), anemia (26%) and rhinitis (23%).

Hirt *et al*. evaluated 25-35 mg/kg TID (all dosed with tablets) in 182 children aged from < 2 months to > 8 years including 82 aged > 2 years.[15] The purpose of this study was to determine if adequate plasma concentrations were achieved with 25-35 mg/kg TID in children using a target Cmin value of 0.8 mg/L. Of the 82 children, 29 aged 2 to 7 years received a mean dose of 416 mg (SD 108) and 53 aged 8 or more received a mean dose of 655 mg (SD 131 mg). The study evaluated % of children with Cmin 0.8 mg/L using Bayesian estimation. In children aged 2 to 16 years who received 25 mg/kg TID the predicted concentration was above 0.8 mg/L in 96% and PK modelling demonstrated that 25-35 mg/kg was optimal for children aged 2 to 13 years. Apparent nelfinavir CLT/F and V/F decreased as a function of age and the authors recommended greater doses for children aged < 2 years.

A prospective cohort evaluated 42 treatment-experienced children who had vertically transmitted HIV.[16] The mean age was 6.7 years, the dose was 25 – 35 mg/kg TID and children were evaluated for a median of 41 months (range 6 to 71.3 months). A virological response (VL < 1 log10) was observed in 38/42 children with an undetectable VL in 28. No significant adverse experiences were observed.

In a study of 615 HIV infected children aged 2 to 12 years on ART in the UK and Ireland between January 1997 and March 2005, it was noted that total doses of 60-90 mg/kg/day were too low and that 62% of children taking nelfinavir were being under-dosed during 1997-1999.[17] The authors noted that with dosing of 110 mg/kg/day, underdosing decreased to 26% in 2000-2002 and to 18% in 2003-2005.

The MAH concluded that a number of studies that evaluated nelfinavir 20-30 mg/kg TID observed low exposures to nelfinavir, significant variability in nelfinavir levels and low virological responses, particularly in smaller and younger children. Some studies that administered this dose targeted the dose to the higher limit of 30 mg/kg TID. In addition, some studies observed correlations between selected PK parameters (AUC_8, Cmin) and suggest that targeted dosing strategies would improve response. However, significant inter-patient variability and low levels have been observed in very young children with doses of approximately 30 mg/kg TID. Increasing the dose to 25-35 mg/kg TID in children ≥ 3 years of age was found to achieve improved virological response rates, did not result in significant changes in AEs and achieved greater exposures in children.

Revision of dosing recommendations in children weighing less than 18 kg

The 250 mg film-coated tablet formulation is approved for use in the age group 3 to 13 years but the existing BID and TID dosing recommendations start at 18 kg.

The WHO weight for height charts for children aged 2 to 5 years cover the weight range 6-27.5 kg (3rd to 97th percentiles) in girls and 6.5-26.5 kg (3rd to 97th percentiles) in boys. As for subjects of < 10 kg body weight the prescriber is currently referred to the SmPC of the oral powder, the MAH initially proposed to introduce tablet dosing recommendations for weight bands 10-12 kg and 13-17 kg to ensure appropriate BID and TID dosing of 250 mg film-coated tablets in children of 10 up to 18 kg body weight.

[15] Age-Related Effects on Nelfinavir and M8 Pharmacokinetics:a Population Study with 182 Children, Deborah Hirt, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2006, p. 910–916

[16] Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children, Salvador Resino, BMC Infectious Diseases 2006, 6:107 doi:10.1186/1471-2334-6-107

[17] Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study, Esse N Menson, BMJ Volume 332, 20 May 2006 bmj.com

During the evaluation of this variation, the MAH proposed in its first response a revised dosing table allowing Viracept 250 mg tablets to be administered in place of oral powder as a TID regimen for children 3 – 13 years of age (Table 7).

BID dose recommendations for the same weight ranges (i.e. <18 kg) were not proposed because the tablets would not achieve the theoretical doses recommended for children in each weight band (based on 50 – 55 mg/kg BID). For example, administration of 1 tablet BID to children with weights between 7.5 kg – 8.5 kg will result in doses of 29.4 - 33.5 mg/kg whereas 2 tablets BID will result in doses of 58.8 – 66.7 mg/kg. Similar problems would arise for the other weight bands as shown in Table 6.

Table 6: Comparison of the calculated dose ranges in mg/kg for BID administration of Viracept 250 mg tablets

Weight Range (kg)	# Tablets/Dose BID	Calculation of dose range that would be provided (mg/kg)	Alternative # Tablets/Dose BID	Calculation of dose range that would be provided (mg/kg)
7.5 – 8.5	2	59 – 67	1	29 – 33
>8.5 – 10.5	2	48 – 59		
>10.5 – 12	2	42 – 48	3	63 – 71
>12 – 14	3	54 – 63	2	36 – 42
>14 – 16	3	47 – 54		
>16 – 18	4	56 – 63	3	42-47
>18 – 22	4	46 – 56		
>22	5	54.3		

The revised dosing table allowing Viracept 250 mg tablets to be administered in place of oral powder as a TID regimen for children 3 – 13 years of age is presented below (Table 7). In order to avoid recommending doses that are lower than the target range, calculations were made to assure that doses of at least 25 mg/kg would be administered for each weight band.

Table 7: Viracept 250 mg tablets based on weight and dose range (25-35 mg/kg TID)

Weight Range (kg)	Lowest Dose mg (25 mg/kg)	Highest Dose mg (35 mg/kg)	Mean Dose	Calculated Mean # 250 mg Tablets (range)	Recommended # 250 mg Tablets per Dose*	Verification of dose range that would be provided (mg/kg)
7.5 – 8.5	188	298	243	0.97 (0.8 – 1.2)	1	29.4 – 33.3
>8.5 – 10.5	213	368	290	1.16 (0.9 – 1.5)	1	23.8 – 29.4
>10.5 – 12	263	420	341	1.37 (1.1 – 1.7)	2	41.7 – 47.6
>12 – 14	300	490	395	1.58 (1.2 – 2.0)	2	35.7 – 41.7
>14 – 16	350	560	455	1.82 (1.4 – 2.2)	2	31.3 – 35.7
>16 – 18	400	630	515	2.06 (1.6 – 2.5)	2	27.8 – 31.3
>18 – 22	450	770	610	2.44 (1.8 – 3.1)	3	34.1 – 41.7
>22	575	805	691	2.76 (2.3 – 3.2)	3	32.6

However, taking equal numbers of tablets for each dose resulted in doses that were either too high or too low in three weight bands, based on the recommended 25 – 35 mg/kg TID (Table 8). Administration of the higher doses was therefore initially proposed by the MAH to assure that adequate doses would be given to children to ensure that the majority of patients receive doses at the upper end of the proposed dose range.

Table 8: Weight bands in which recommended doses were either too high or too low

Weight bands	Dosing schedule	Too high to be within the 25-35 mg/kg/dose	Dosing schedule	Too low to be within the 25-35 mg/kg /dose
>10.5-12	2 tab TID	41.6-47.7	1 tab TID	20.8-23.8
>12-14	2 tab TID	35.7-41.7	1 tab TID	17.9-20.8
>18-22	3 tab TID	34.1-41.7	2 tab TID	22.7-27.7

Studies demonstrated that significant inter-patient variability in plasma levels have been observed with administration of different doses of Viracept to children. In the AG1343-556 study, very low and high exposures to nelfinavir were observed in children who received 25-35 mg/kg TID doses. The higher doses recommended in some of the weight bands would assure that adequate doses and optimal exposures to nelfinavir would be achieved, while data on higher exposures in these weight bands did not reveal any additional safety concerns based on studies including the AG1343-556 study. However, these higher doses were based on theoretical calculations that had not been evaluated in children.

Following the CHMP concern that the revised recommendations for TID dosing with tablets appear to be potentially sub-optimal in some weight bands the MAH reassessed all available data at the high end of TID dosing. Data were available from children receiving high nelfinavir doses on a twice daily regimen (50 – 55 mg/kg). However, there were limited data available for doses > 35 mg/kg administered three times daily in children 3 – 13 years of age. Specifically, in the AG1343-556 study, doses were greater than 25 – 35 mg/kg in 6 patients and the highest dose of 38.2 mg/kg was administered to 2 children in the study (Table 9). Of the 6 children with doses >35 to 38.2 mg/kg/dose, 5 children were in the >12-14 weight band and none were in either the >10.5 - 12 kg or the >18 – 22 kg weight bands.

Table 9: Range doses > 35 mg/kg administered to children in the AG1343-556 study

AG1343-556 Children with Doses > 35 mg/kg				
Patient ID #	Age (Yrs)	Baseline Weight (Kg)	Dose – Low Range* (mg/kg)	Dose – High Range* (mg/kg)
2402	3.5	13.1	32.68	38.16
2702	3.3	13.3	32.68	38.16
1304	3.0	14.2	31.05	35.21
2805	3.0	14.2	30.3	35.71
2820	3.4	14.2	27.17	35.21
2801	4.1	15.8	28.48	35.21

AG1343-556 clinical study report; Appendix, Patient Listing 32

*Dose range represents the lowest and highest doses in mg/kg taken by each study subject during the study.

The potential benefits for using equal doses exceeding the upper range of 35 mg/kg in three weight bands include avoidance of under dosing and theoretically, limiting HIV-1 resistance and potential virological rebound.

The risks for children in three weight bands that would receive > 35 mg/kg include potential increases in frequency and/or severity of adverse events, intolerance to the medication, interruption of dosing associated with adverse events, the development of HIV-1 resistance and potential virological rebound due to reduced tolerability. Long term overdosing may occur for children who remain in one of the three weight bands for extended periods of time and would take doses > 35 mg/kg TID long term. However, the potential consequences of long term overdosing have not been evaluated.

Children in the two lowest weight bands may be exposed to higher doses for limited periods of time. Children with weights 10.5 – 12 kg and 12 – 14 kg would be expected to remain in these weight bands for approximately 7.5 - 10 months and 12 - 14.5 months, respectively. However, according to the growth charts for healthy children, most children with weights 10.5 – 12 kg would be 3 years of age or less. Healthy children with weights 18 – 22 kg would be 5 – 6.5 years of age and estimates suggest that children may remain within this weight band for 18 – 20 months.

In conclusion, having reviewed all the data, the MAH revisited the proposal made in response to the second request for supplementary information in which unequal doses over each day were proposed to achieve a total daily dose that would be consistent with that provided by 25 – 35 mg/kg TID and without exceeding 35 mg/kg. This dosing regimen is consistent with the daily doses that documented the efficacy and safety of nelfinavir in paediatric clinical trials (see Table 10).

Table 10: Viracept 250 mg tablets TID (25-35 mg/kg TID)

Dose to be administered three times a day to children aged 3 to 13				
Body weight of the patient in kg	Recommended number of tablets at each meal			Total number of tablets per day
	Number of tablets at breakfast	Number of tablets at lunch	Number of tablets at dinner	
7.5 to 8.5 kg	1	1	1	3
8.5 to 10.5 kg	1	1	1	3
10.5 to 12 kg*	2	1	1	4
12 to 14 kg*	2	1	2	5
14 to 16 kg	2	2	2	6
16 to 18 kg	2	2	2	6
18 to 22 kg*	3	2	2	7
over 22 kg	3	3	3	9

*: Children with these weights will be given an uneven number of tablets during the day.

Within the constraints of a fixed 250 mg tablet strength and a fixed TID dosing frequency, it is not possible to design a dose regimen that uses an equal number of tablets per dose that satisfies the established dose range. Evidence for the appropriateness of targeting a daily dose comes from the approved BID and TID regimens used for nelfinavir, both of which have the same upper target for the daily dose (~105-110 mg/kg/day).

The variable dosing with the TID regimen should not lead to sub therapeutic concentrations of nelfinavir in children because the elimination half life of nelfinavir is 3.5 – 5 hours and due to the presence of the active metabolite (M8) that contributes to antiviral activity (ratio of M8:nelfinavir exposure is approximately 1:3).

In study AG1343-556 viral suppression was maintained more frequently in patients with an estimated AUC of at least 12.5 pg*hr/mL (54% response) compared to those with an AUC of less than 12.5 pg*hr/mL (28% response) but the PACTG 377 study that evaluated nelfinavir 30 mg/kg TID did not find a relationship between Cmin and virological response. There were significant differences between patients in Cmin values which further demonstrates the inter-patient variability in the PK of nelfinavir and difficulty in correlating virological response to Cmin.

The MAH has evaluated alternative ways that would allow administration of 250 mg tablets on a TID regimen. The MAH looked at calculations using half tablets with a TID equal dosing regimen in the three weight bands and found that the doses were close to the 35 mg/kg/dose limit (Table 11).

Table 11: Dose recommendations within target range using half tablets

Weight bands	Dosing schedule	Total number of tablets per day	Mg/kg/dose
>10.5 - 12 kg	1.5 tab TID	4.5	31.3 - 35.7
>12 - 14 kg	1.5 tab TID	4.5	26.8 - 31.3
>18 - 22 kg	2.5 tab TID	7.5	28.4 - 34.7

However, Viracept tablets cannot be cut in half and there is no possibility to achieve the dosing schedule to administer equal numbers of whole tablets on a TID basis. In addition, there is no method that would allow accurate measurements of partial quantities of crushed tablets to children. Therefore, there is no method that would allow equal dosing of whole tablets three times daily using 250 mg tablets that would adhere to the 25 – 35 mg/kg TID dosing schedule.

In another scenario, the observation was made that adding 3 half tablets within a 24 hour period is equivalent to one whole and one half tablet during the day. Doses were recalculated on a daily basis and the extra half tablet doses were rounded up or down to result in doses as close as possible to the target doses using whole 250 mg tablets (Table 12).

Table 12: From half to whole tablets

Weight bands	Dosing schedule for equal whole tablets TID	Additional whole tablets by rounding up or down per day	Total Tablets per day
>10.5-12	1 tab tid	Plus 1	4
>12-14	1 tab tid	Plus 2	5
>18-22	2 tab tid	Plus 1	7

The MAH has acknowledged that this dosing schedule represents an unequal number of whole tablets given during the day but it eliminates the half tablet dilemma and provides a practical way to administer the recommended doses on a daily basis.

The highest dose administered at breakfast would be separated as far apart as possible from the high dose administered during dinner (for the 12 – 14 mg/kg weight band). An alternative scenario of giving dispersed tablets at bedtime would result in another meal before going to bed. This scenario is not acceptable because it results in a four times a day regimen and there is no data for QID dosing in children. Therefore, the following TID regimen is proposed for the particular 3 weight bands affected (Table 13).

Table 13: Dose recommendations for each meal

Weight bands in kg	Breakfast	Lunch	Dinner
>10.5 - 12	2 tab	1 tab	1 tab
>12 - 14	2 tab	1 tab	2 tab
>18 - 22	3 tab	2 tab	2 tab

The paediatric dose is based on an average daily dose that falls within the range that was established for safety and efficacy in paediatric studies (Table 14). Clinical experience with BID and TID dosing regimens, both of which target an average upper daily dose of roughly 105 to 110 mg/kg have shown similar safety and efficacy.

Table 14: Dose recommendations with average dose ranges

Weight bands in kg	Breakfast	Lunch	Dinner	Average dose range in mg/kg/dose	
>10.5 - 12	2 tab	1 tab	1 tab	27.8-31.7	Within limits
>12 - 14	2 tab	1 tab	2 tab	29.8-34.7	Within limits
>18 - 22	3 tab	2 tab	2 tab	26.5-32.4	Within limits

Therefore, the MAH considered that the proposed unequal dosing table for Viracept 250 mg tablets administered as a TID regimen is the optimal dosing recommendation for Viracept in children < 22 kg. This dosing schedule is consistent with total daily doses of nelfinavir that have been evaluated in paediatric trials. Unequal dosing with the TID regimen does not appear to be more difficult or error prone than the current powder instructions that recommend using two different size scoops.

According to the MAH, an alternative option would be preclusion of all use of tablets in children in less then 22 kg. This would apply to children of approximately 6.5 years of age upwards**.** Children with weights < 22 kg would have the option of initiating other protease inhibitors. Initiating antiretroviral therapies other than Viracept would be consistent with current HIV treatment guidelines in children. However, the protease inhibitors that are recommended for children consist of ritonavir boosted agents (e.g. ritonavir boosted lopinavir, darunavir or fosamprenavir). Nelfinavir provides an option of a PI that does not require co administration with ritonavir. In addition, the studies provided have demonstrated the efficacy of nelfinavir-containing HAART in children ≥ 3 years of age.

Bioequivalence between nelfinavir tablets and nelfinavir powder

The original MAA stated that similar plasma concentration-time profiles were demonstrated for single doses of Viracept tablets and powder. This was based on the findings of the Agouron AG1343-524 study that evaluated the single dose PK profile of nelfinavir powder administered to children from 0-13 years of age and the relative bioavailability of nelfinavir oral powder versus tablets in HIV infected

children aged 7 to 13 years. The results demonstrated that the PK of nelfinavir tablets and powder were comparable. Viracept doses of 20 to 30 mg/kg three times daily (TID) in children aged 2 to 13 years achieved plasma concentrations comparable to those in adults receiving a 750 mg TID regimen. The purpose of this early paediatric study was to determine the appropriate dose of oral powder in HIV-infected children and exposed infants. The study was not designed to assess bioequivalence.

Bioequivalence between the tablet and powder formulations was evaluated in the BE study (AG1343-550) conducted by Agouron/Pfizer in the U.S. in 1997. This randomised, open label, cross over study enrolled 19 and evaluated 18 healthy adult volunteers. Each subject received a single dose of nelfinavir 750 mg on two occasions (as tablets and as powder) separated by a 3-7 day washout period. Dosing was with a standardised breakfast and blood samples were collected prior to and at specific times up to 24 hours after the dose. PK parameters were calculated using noncompartmental methods and comparisons between formulations employed ANOVA with a 2-way crossover model. GMRs and 90% CI were computed using the LSM analysis of log-transformed PK parameters with results as shown in Table 15.

Table 15: Summary of statistical comparison of tablet and powder pharmacokinetics

	All Subjects				Excluding Subject #20	
PK Parameter	TABLET Geometric LS Mean (95% CI)	POWDER Geometric LS Mean (95% CI)	Geometric Mean Ratio (90% CI)	ANOVA p-Value for Treatment Difference	Geometric Mean Ratio (90% CI)	ANOVA p-Value for Treatment Difference
AUC_{∞} (µg*Hr/mL)	29.9 (28.0 – 31.9)	30.9 (29.0 – 33.0)	1.03 (0.96 – 1.12)	0.4625	1.02 (0.95 – 1.11)	0.6089
AUC_{last} (µg*Hr/mL)	28.1 (26.4 – 30.0)	30.3 (28.4 – 32.3)	1.08 (1.00 – 1.16)	0.1022	1.05 (0.98 – 1.13)	0.2002
C_{max} (µg/mL)	2.97 (2.69 – 3.28)	3.46 (3.13 – 3.83)	1.17 (1.04 – 1.31)	0.0370	1.10 (1.03 – 1.18)	0.0249
T_{max} (Hr)[a]	6.00 [a] (4.00 – 12.00)	4.25 [a] (3.50 – 6.00)	-1.00 [b] ((-3.00) – (-1.00))	0.0005	-1.00 [b] ((-3.25) – (-1.00))	0.0006
T ½ (Hr)	4.25 (3.66 – 4.93)	3.29 (2.84 – 3.82)	0.78 (0.65 – 0.92)	0.0213	0.84 (0.75 – 0.94)	0.0138

From AG1343-550 Clinical study report

[a] Median (range)

[b] Median difference reported instead of geometric mean ratio. Analysis of p-value is from Wilcoxon Rank-Sum test

AUC_{∞} - Area under the plasma concentration curve extrapolated to infinite time

AUC_{last} Area under the plasma concentration curve extrapolated to the last measurable time point

C_{max} – Maximum plasma concentration

T_{max} – Time to maximum plasma concentration

$T_{1/2}$ - Plasma concentration half life

There were no statistically significant difference between formulations for nelfinavir AUC∞ and AUClast and the 90% CI around the GMR fell within the required range. Cmax was marginally greater for the oral powder with 90% CI that did not span zero and with an upper limit that exceeded the

requirement. The median Tmax occurred earlier after dosing with powder and the geometric mean T½ was slightly shorter. Although these differences were modest the differences between the formulations for Tmax and T½ were statistically significant ($p < 0.05$).

The plasma concentration profile of the tablet formulation in one subject was significantly different versus all other subjects with a low Cmax (1.06 µg/mL vs. 1.89–5.84 µg/mL) and also lower than the Cmax for the same subject after taking the powder (3.22 µg/mL). This subject also had a lower post-tablet AUClast (17.67 µg*hr/mL) versus mean AUClast 29.9 µg*hr/mL and a value of 22.33 µg*hr/mL for this subject after dosing with powder. The plasma T½ (12 hrs) after the tablets was higher than in other subjects (mean 4.25 hrs) and greater than the half life observed after dosing with powder (2.74 hr). When data from this one subject were excluded from the analysis of Cmax, the 90% CI of 1.03 – 1.18 was within the required range.

Acceptability of crushed tablets and tablets dispersed in water

The MAH has proposed administration of tablets, dispersed in water for children who are unable to swallow whole tablets.

This proposal was based upon practice derived from clinical studies and as being practiced based upon recommendation in the US product information as well as known to be practiced on a off label use. As per CHMP request, the MAH has also evaluated alternative options to the crushing. The current formulation of the Viracept film coated tablets was not designed to be chewed. The force needed for chewing the film coated tablets is very high and may result in damage to children's teeth. The MAH has not encountered individuals chewing tablets in any clinical studies and there is no information on the tolerability of chewing tablets in either adults or children. The MAH considers this alternative for patients unable to swallow tablets as not a suitable option.

In addition, the MAH determined from internal testing that insertion of tablets in 100 ml water followed by continuous stirring for approximately 3 minutes resulted in a suspension that could be consumed by children. Mixing and dispersing Viracept tablets in a small amount of water is recommended as an alternative to oral powder in children. Tablets should be dispersed in 100 ml (~½ cup) water and stirred thoroughly for approximately 3 minutes with a spoon until dispersed. Then the cloudy bluish liquid should be consumed. As parts of the film-coated tablet formulation are insoluble in water, some particles will sediment and will remain at the bottom of the glass. Another 100 ml (~ ½ cup) of water should be used to rinse the remaining suspension and consumed.

Viracept as crushed tablets have been administered to adults and to children for a number of years. There have been no formal study that has specifically compared the taste or tolerability of crushed tablets compared to whole tablets. However, administration of Viracept whole or crushed tablets dispersed in water has been evaluated in clinical studies in healthy volunteers and in HIV infected patients. Most results concluded that either there was no taste or that the crushed tablets were well tolerated.

One study evaluated the effect of 4 protease inhibitors including nelfinavir, indinavir, ritonavir and saquinavir on the sense of taste in 14 untreated HIV infected adults and in 46 healthy volunteers. Measured samples of the protease inhibitors were mixed with water or with ethanol and were placed on the tongues of study subjects to determine the effects of these drugs on the taste of different substances and analysed. The taste of the three protease inhibitors (indinavir, ritonavir, saquinavir) were found to be predominantly bitter while nelfinavir was found to be relatively tasteless. The authors noted that nelfinavir dispersed in water was tasteless because it is not soluble in water.

Another study compared the pharmacokinetic profile of single dose Viracept 250 mg tablets with tablets administered as a suspension to 12 healthy volunteers in a single dose, randomised, two-way crossover study. The suspension was prepared by dispersing 5 tablets in 100 ml water at room temperature for a few minutes prior to administration. An additional 50 ml of water was used to mix with and consume the residual suspension if necessary. The authors noted that the suspension and tablets were well tolerated without major or unexpected complications. The authors also stated that the nelfinavir suspension resulted in a "tasteless formulation that was easy to swallow".

The Penta 7 trial evaluated nelfinavir in 20 young infants (median age 2.5 months). Viracept oral powder was available for children at the start of the study. The authors noted that because of the difficulty of administering the powder to infants, all children were switched to Viracept tablets that were crushed and administered as a suspension.

Another study evaluated the pharmacokinetics of nelfinavir in 182 children with a median age of 8.2 years (range: 3 days to 17 years). In this study, nelfinavir was administered according to body weight as only 250-mg tablets and tablets were "crumbled in a small volume of water and added to milk or food" when children could not swallow whole tablets. The authors noted that nelfinavir was tolerated by children in this study.

A number of other paediatric studies that evaluated nelfinavir replaced oral powder with tablets (dissolved in liquid) due to poor palatability of the oral powder and to improve tolerability and assure adherence. In addition, crushed tablets are recommended in HIV treatment guidelines for children.

Discussion

The MAH submitted the full set of clinical study reports and a literature review which was performed to provide further evidence supporting the change in the TID dosing recommendation for children aged 3-13 years from 25-30 mg/kg to 25-35 mg/kg. The MAH submitted the full set of clinical study reports and performed a literature review to assess all relevant published data and experience accumulated in children.

The initial studies that evaluated nelfinavir in children at doses in the range of 20-30 mg/kg TID suggested that, based on small numbers, this dose range might be adequate. However, some subsequent studies described variability in virological response rates and in plasma levels, particularly in young children. Doses in the range 25-35 mg/kg TID may improve plasma exposure and virological response rates. Not all of the data have indicated a strong relationship between plasma exposure and virological response rates but this may be due to timing and sparsity of samples rather than lack of any relationship, which would seem unlikely. Therefore, the MAH's proposal to increase the TID dose regimen to 25-35 mg/kg is considered acceptable by CHMP.

In considering the proposals for adding dose recommendations for tablets for children aged 3-13 years weighing less than 18 kg the MAH was also requested to provide further reassurance on the bioequivalence of the tablets and oral powder. The MAH made reference to study AG1343-550 which evaluated bioequivalence between the tablet and powder formulations conducted in 1997. Study AG1343-550 essentially demonstrates bioequivalence with the exception of Cmax in the primary analysis but it seems unlikely that the difference in Cmax observed would have much relevance to long-term efficacy of a protease inhibitor.

Regarding the proposed dose recommendations for tablets for children aged 3-13 years weighing less than 18 kg, the CHMP considers that the final proposal of the MAH (which includes unequal numbers of tablets at each daily dose for three weight ranges) is likely the best compromise. Some concern regarding the potential for confusion and over dosing remains but the CHMP considers that caregivers for these children given the total complexities of treatment regimens are likely well attuned to dosing issues.

Studies that evaluated crushed tablets and tablets dispersed in water and administered to children revealed that either there was no taste or that the crushed tablets were well tolerated. Therefore compared to the powder formulation, Viracept tablets that were crushed or dispersed in water did not result in noncompliance due to intolerability or to bitter taste and they may be more convenient for the patients. There is a recognised risk of potential loss of tablet particles during the crushing of the tablet if not performed with adequate tools (e.g. mortar and pestle, spoon, etc.), however chewing of tablets cannot be recommended as an option. Therefore the MAH's proposed recommendations appear to be suitable to ensure that the crushed tablet dose is consumed.

Finally the MAH provided information about the use of nelfinavir oral powder in ARV therapy in children. Many physicians have reported that this formulation is not well accepted by children. The current variation sought to provide the option of using Viracept tablets that can be dispersed in water for HIV infected children 3 – 13 years of age. While it may be little used there could be some children for whom this still represents an option.

Changes to the product information

Following the CHMP discussion as detailed above, changes have been proposed in section 4.2 of the SmPC and accordingly reflected in the PL:

- *Oral Powder 50 mg/g – section 4.2 of SmPC*

Patients aged 3 to 13 years: for children, the recommended starting dose is 50-55 mg/kg BID or if using a TID regimen, 25 – ~~30~~ **35** mg/kg body weight per dose.

…

Dose to be administered three times a day to children aged 3 to 13				
Body ~~W~~**w**eight of the patient in kg	Blue Scoop 5 gram		White Scoop 1 gram	Total grams of Powder per dose
7.5 to 8.5 kg	**1** ~~=~~		~~4~~	**5** ~~4~~ g
8.5 to 10.5 kg	1	**plus**	**1** ~~-~~	**6** ~~5~~ g
10.5 to 12 kg	1	plus	**2** ~~1~~	**7** ~~6~~ g
12 to 14 kg	1	plus	**3** ~~2~~	**8** ~~7~~ g
14 to 16 kg	**2** ~~1~~	~~plus~~	~~3~~	**10** ~~8~~ g
16 to 18 kg	**2** ~~1~~	plus	**1** ~~4~~	**11** ~~9~~ g
18 to 22 kg	2	plus	**3** ~~-~~	**13** ~~10~~ g
over 22 kg	3		-	15 g

- *Film-coated tablets 250 mg – section 4.2 of the SmPC*

Patients aged 3 to 13 years: for children, the recommended starting dose is 50-55 mg/kg BID or if using a TID regimen, 25 – ~~30~~ 35 mg/kg body weight per dose. ~~For children unable to take tablets, VIRACEPT oral powder may be administered instead (see Summary of Product Characteristics for VIRACEPT oral powder).~~

The recommended dose of VIRACEPT film-coated tablets to be administered BID to children aged 3 to 13 years is as follows:

Dose to be administered two times a day to children aged 3 to 13	
Body ~~W~~**w**eight of the patient in kg	Number of VIRACEPT 250 mg film-coated tablets per dose*
18 to 22 kg	4
over 22 **kg**	5

The recommended dose of VIRACEPT film-coated tablets to be administered TID to children aged 3 to 13 years is **shown in the table below**. ~~as follows:~~ **Children with weights between 10.5–12 kg, 12–14 kg and 18–22 kg will receive a different number of tablets with each meal. The table provides a schedule assuring that the appropriate total daily dose of Viracept is taken each day based on the child's weight.**

The prescriber should advise the caregiver to carefully monitor increases in weight of the child to ensure that the appropriate total daily dose is taken. The prescriber should also advise the caregiver about the importance of adhering to the dosing instructions and that the appropriate number of tablets should be taken at each dose with a meal.

~~Dose to be administered three times a day to children aged 3 to 13~~	
~~Body Weight of the patient in kg~~	~~Number of VIRACEPT 250 mg film-coated tablets per dose*~~
~~18 to 22 kg~~ ~~over 22~~	~~2~~ ~~3~~

~~*see Summary of Product Characteristics for VIRACEPT oral powder for patients with less than 18 kg body weight.~~

Dose to be administered three times a day to children aged 3 to 13				
Body weight of the patient in kg	**Recommended number of tablets at each meal**			**Total number of tablets per day**
	Number of tablets at breakfast	**Number of tablets at lunch**	**Number of tablets at dinner**	
7.5 to 8.5 kg	**1**	**1**	**1**	**3**
8.5 to 10.5 kg	**1**	**1**	**1**	**3**
10.5 to 12 kg*	**2**	**1**	**1**	**4**
12 to 14 kg*	**2**	**1**	**2**	**5**

14 to 16 kg	**2**	**2**	**2**	**6**
16 to 18 kg	**2**	**2**	**2**	**6**
18 to 22 kg*	**3**	**2**	**2**	**7**
over 22 kg	**3**	**3**	**3**	**9**

*** Children with these weights will be given an uneven number of tablets during the day. The virologic and immunologic responses should be monitored to assure these children achieve response to therapy.**

For patients unable to swallow the tablets, VIRACEPT tablets may be dispersed in a half cup of water while thoroughly stirring with a spoon. Once dispersed, the cloudy bluish liquid should be thoroughly mixed and consumed immediately. The glass should be rinsed with a half cup of water and the rinse should be swallowed to ensure that the entire dose is consumed.

Acidic food or juice (e.g. orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. The VIRACEPT suspension should be taken with a meal.

The prescriber should assure that the caregiver understands the importance of monitoring adherence and the appropriate method to prepare and administer Viracept tablets to children in each weight band.

- *Oral Powder 50 mg/g – section 3 of the Package Leaflet*

The different ways are shown in separate tables below.

- Table 2: if you give the medicine two times a day, you will give 50-55 mg nelfinavir each time for each kg of body weight.
- Table 3: if you give the medicine three times a day, you will give 25-3**5**~~0~~ mg nelfinavir each time for each kg of body weight.

…

Dose to be given three times a day to children aged 3 to 13				
Body weight of your child	Number of scoops Blue Scoop (5 g)		White Scoop (1 g)	How much to give each time (in grams)
7.5 to 8.5 kg	**1** ~~=~~		~~4~~	**5** ~~4~~ g
8.5 to 10.5 kg	1	**plus**	**1** ~~-~~	**6** ~~5~~ g
10.5 to 12 kg	1	plus	**2** ~~1~~	**7** ~~6~~ g
12 to 14 kg	1	plus	**3** ~~2~~	**8** ~~7~~ g
14 to 16 kg	**2** ~~1~~	~~plus~~	~~3=~~	**10** ~~8~~ g
16 to 18 kg	**2** ~~1~~	plus	**1** ~~4~~	**11** ~~9~~ g
18 to 22 kg	2	plus	**3** ~~-~~	**13** ~~10~~ g
over 22 kg	3		-	15 g

- *Film-coated tablets 250 mg – section 3 of the Package Leaflet*

The Viracept tablets must be taken by mouth. They should be swallowed whole and ~~should be~~ taken with a meal. For adults or children unable to take tablets, **Viracept tablets may be put into water and taken as follows:**

- **Put the tablets in a half cup of water and stir with a spoon.**
- **Once the tablet is dispersed, mix the cloudy bluish liquid thoroughly and take immediately.**
- **Rinse the glass with a half cup of water and swallow the rinse to ensure all of the dose is taken.**

Acidic food or juice (such as orange juice, apple juice or apple sauce) are not recommended to be taken with Viracept because together they may have a bitter taste.

Alternatively, Viracept 50 mg/g oral powder may be taken instead. If you want to take the powder instead please see the Package Leaflet for Viracept 50 mg/g oral powder~~)~~.

…

Children aged 3 to 13 years
For children aged 3 to 13 years, the recommended dose of Viracept tablets is based on their body weight. **Carefully monitor the increase in weight of your child to ensure the appropriate total daily dose is taken.** ~~You will either give the medicine to your child two or three times a day with a meal.~~

- **When your child weighs 18 kg or more, you may provide the tablets either two or three times a day.**
- **When your child weighs 18 kg or less, you must provide the tablets three times a day.**

The different ways are shown in separate tables below.

- Table 2: if you give the medicine two times a day **(for children who weigh 18 kg or more)**, you will give 50-55 mg nelfinavir each time for each kg of body weight.
- Table 3: if you give the medicine three times a day, you will give 25-3**5**~~0~~ mg nelfinavir each time for each kg of body weight**, except for children who weigh from 10.5 to 12 kg, from 12 to 14 kg and from 18 to 22 kg. These children will be given a different number of tablets with each meal. The table also shows the recommended total number of Viracept tablets that children will be given each day based on their weight.**

Table 2

Dose to be given two times a day to children aged 3 to 13 **who weigh more than 18 kg** ~~years*~~	
Body ~~W~~**w**eight of your child	Number of tablets
18 to 22 kg	4
over 22 kg	5

~~Table 3~~

~~Dose to be given three times a day to children aged 3 to 13*~~	
~~Body Weight of your child~~	~~Number of tablets~~
~~18 to 22 kg~~	~~2~~
~~over 22 kg~~	~~3~~

~~*see Package Leaflet for Viracept oral powder for children less than 18 kg body weight.~~

Table 3

Dose to be given three times a day to children aged 3 to 13 who weigh more than 7.5 kg				
Body weight of your child	**Recommended number of tablets given at each meal**			**Total number of tablets per day**
	Number of tablets at breakfast	**Number of tablets at lunch**	**Number of tablets at dinner**	
7.5 to 8.5 kg	**1**	**1**	**1**	**3**
8.5 to 10.5 kg	**1**	**1**	**1**	**3**
10.5 to 12 kg*	**2**	**1**	**1**	**4**
12 to 14 kg*	**2**	**1**	**2**	**5**
14 to 16 kg	**2**	**2**	**2**	**6**
16 to 18 kg	**2**	**2**	**2**	**6**
18 to 22 kg*	**3**	**2**	**2**	**7**
over 22 kg	**3**	**3**	**3**	**9**

*** Children with these weights will be given an uneven number of tablets during the day. Your doctor should monitor the number of HIV particles and the number of CD4 white blood cells in your child's blood to assure the medicine works as well as it can.**

It is very important that the correct number of tablets be taken at each dose. You should monitor your child to assure that the recommended number of tablets are taken at each dose with meals, for each weight band.

The MAH has also taken the opportunity to update Annex II with the current PSUR cycle and to update the details of the Cyprus local representatives in the package leaflet.

The CHMP considered the proposed changes to the Summary of Product Characteristics, Annex II and Package Leaflet be acceptable.

2. Conclusion

On 21 July 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted).