CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-503

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-503
Submission Dates:	07/03/2002, 04/11/2003, and 04/14/2003.
Brand Name:	Viracept®
Generic Name:	nelfinavir mesylate
Indication:	Treatment of HIV-1 infection
Applicant:	Agouron Pharmaceuticals, Inc.
Formulation:	625 mg Tablets
Pharmacometrics Reviewer:	Jenny J. Zheng, Ph.D.
Reviewer:	Robert O. Kumi, Ph.D.
Team Leader:	Kellie Reynolds, Pharm.D.
OCPB Division:	DPE III
OND Division:	Division of Antiviral Drug Products
Draft Review Dates:	04/04/2003 and 04/17/2003

I. Executive Summary

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to Section 6 of NDA 21-503 (Viracept, nelfinavir mesylate). The information provided on the new 625 mg tablet adequately addresses the requirements of 21 CFR Part 320 and is sufficient to make labeling recommendations related to clinical pharmacology, biopharmaceutics and pharmacokinetics.

Recommendations

New 625 mg tablet Formulation

The information provided in NDA 21503 supports the applicant's labeling proposals for the new 625 mg tablet. Two bioequivalence studies (Studies 712 and 713), exposure- response analyses and dissolution information were provided and reviewed.

- Bioequivalence

In both bioequivalence (BE) studies, the 625 mg tablet (test) was not bioequivalent to the marketed 250 mg tablet (reference); nelfinavir exposure with the 625 mg tablet was 15 to 32 % greater than that with the 250 mg tablet following single dose administration (1250 mg). Because the 625 mg tablet was not bioequivalent to the 250 mg tablet, an exposure-response analysis was conducted to determine the clinical effect of a higher nelfinavir exposure.

- Exposure-Response Analyses

The applicant and Pharmacometrics (PM) Reviewer conducted exposure-response analyses to determine the potential clinical impact of increased nelfinavir exposure (625 mg tablet vs. 250 mg tablet). Both analyses showed a relationship between nelfinavir exposure (AUC) and response (diarrhea). The PM review indicated that at the 1250 mg BID dose, subjects receiving the 625 mg tablet had a 6 % higher probability (based on mean values) of having diarrhea than subjects receiving the 250 mg have tablets. According to the applicant, because diarrhea is clinically manageable and commonly encountered during anti-HIV therapy, the 625 mg tablet can be used in the 1250 mg BID nelfinavir regimen. The Clinical Division agrees with the applicant's assessment.

- Dissolution

The applicant provided sufficient dissolution information to select a dissolution method and to set a dissolution specification. Dissolution of the 625 mg tablet was evaluated under varying conditions (different media, paddle rotation speed, and vessels). Based on evaluation of the dissolution data, the dissolution method and specification for the 625 mg tablet are:

Dissolution Method

Dissolution medium	0.1 N HCl
Paddle Speed	50 rpm
Vessel	Standard

Dissolution Specification

Q = ⁄ % in 45 minutes

Role of CYP2C19 in Nelfinavir Metabolism

The information provided by the applicant regarding the role of the CYP2C19 enzyme in nelfinavir metabolism is adequate to make changes to the Viracept label. The information comprises previously reviewed *in vitro* metabolism data (Clinical Pharmacology review for NDA 20-779) and newer drug-drug interaction information (delavirdine-nelfinavir and ritonavir-nelfinavir). The *in vitro* metabolism data indicated that the enzymes responsible for nelfinavir metabolism had the following order of potency: CYP3A > CYP2C19 > CYP2D6 > CYP2C9. *In vivo* drug-drug interaction and metabolism data showed that delavirdine (CYP3A and CYP2C19 inhibitor) inhibited nelfinavir metabolism to a greater extent than ritonavir (CYP3A inhibitor). Collectively, the *in vitro* and *in vivo* findings indicate that the CYP2C19 enzyme plays a major role in the metabolism of nelfinavir. This new metabolism information should be included in the nelfinavir label.

_____ Date_____

Robert O. Kumi, Ph. D.
Clinical Pharmacology Reviewer

_____ Date_____

Kellie Reynolds, Pharm. D.
Clinical Pharmacology Team Leader

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background and Rationale

Nelfinavir mesylate is an HIV-1 protease inhibitor that is indicated for the treatment of HIV in combination with other antiretroviral agents. Nelfinavir (NFV) is given as 250 mg tablets in a 1250 mg twice daily (BID) or 750 mg three times daily (TID) regimen. The applicant intends to introduce a new 625 mg tablet that will be used in the 1250 mg BID regimen. Potentially, the 625 mg tablet will increase patient compliance, as patients will take two vs. five tablets per dose.

Drug-drug interaction information for nelfinavir-ritonavir and nelfinavir-delavirdine were included in the current submission to provide pharmacokinetic (PK) and safety information at high NFV exposure and to support the role of CYP2C19 in NFV metabolism. The applicant does not intend to include this drug-drug interaction information in label currently; consequently, these drug-drug interaction studies were not reviewed in detail. Exclusion of this drug-drug interaction information is acceptable because the Viracept label already has ritonavir-nelfinavir and delavirdine-nelfinavir drug-drug interaction information. Furthermore, the new data will not provide specific dosing information for the described drug combinations. In a previous submission (NDA 20779 SLR 039), the applicant indicated that "nelfinavir is metabolized by CYP3A and CYP2C19 (at approximately equal proportion) in humans", but this information was not in the Viracept label. Consequently, in the current submission, the applicant provided supporting information to reflect the contribution of CYP2C19 to nelfinavir metabolism.

Clinical pharmacology and biopharmaceutical studies included in NDA 21-503 are summarized in the table below.

Study Identifier	Brief Description/Title
Evaluation of Bioequivalence	
Study 712	Bioequivalence assessment of 625 mg tablet vs. 250 mg table (fasted state)
Study 713	Bioequivalence assessment of 625 mg tablet vs. 250 mg table (fed state)
Evaluation of CYP2C19 contribution to Nelfinavir Metabolism	
M/331/0070	Nelfinavir 750 mg TID + Delavirdine 400 mg TID
M/331/0073A	Nelfinavir 750 mg TID + Delavirdine 400 or 600 mg TID
Study 711	Nelfinavir 1250 mg BID + Delavirdine 600 mg BID
Evaluation of Dissolution	
	Dissolution data for BE studies

Summary of Key Bioequivalence, Drug-Drug Interaction and Metabolism, and Biopharmaceutical Information

- In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation under fasted or fed conditions. In the fasted state (n = 27), the AUC and C_{max} were 32 % and 24 % higher, respectively, for the 625 mg tablet compared to the 250 mg tablet. In the fed state (n =28), the AUC and C_{max} were 24 % and 15 % higher, respectively, for the 625 mg tablet compared to the 250 mg tablet.
- Based on the exposure-response analyses, the incidence of diarrhea in subjects receiving the 625 mg tablet is approximately 6 % greater than in subjects receiving the 250 mg tablet at a 1250 mg twice-daily dose
- *In vivo*, nelfinavir is metabolized primarily by CYP3A and CYP2C19
- Delavirdine inhibits nelfinavir metabolism to a greater extent than ritonavir; the increased inhibition by nelfinavir is likely due to inhibition of CYP2C19 in addition to CYP3A.
- Based on a cross-study comparison (Study 713 vs. 712), food increases nelfinavir AUC and C_{max} by 2-3-fold following administration of the 250 mg and 625 mg tablets. The pharmacokinetic variability in the fasted state (> 50 %) is greater than that in the fed state (< 40 %).

IV. Question Based Review (QBR)

An abridged version of the Question Based Review (QBR) was employed for this review because the submission (NDA 21-503) focuses on the new 625 mg tablet. For additional background information on nelfinavir, please refer to the Clinical Pharmacology and Biopharmaceutics Reviews for NDA 20-779 and NDA 20-778.

The four main QBR areas addressed in this review are as follows:

1. General Attributes (Characteristics of 625 mg Formulation)
2. General Clinical Pharmacology (Exposure-Response)
3. Extrinsic and Intrinsic Factors (Drug Interactions and Genetic Polymorphism)
4. Biopharmaceutics (Bioequivalence, Food and Dissolution)

What are the general attributes of the proposed 625 mg tablet?

The 625 mg nelfinavir mesylate tablets are immediate release tablets, and have the same chemistry manufacturing and controls processes as the marketed 250 mg tablets. The 625 mg tablets are white and have an oval shape. The main differences between the 625 mg tablet and the 250 mg tablets are as follows: 1) addition of colloidal silicon dioxide — 625 mg tablet) and 2) deletion of FD&C Blue — dye (625 mg tablet).

The quantitative composition of the proposed 625 mg tablets (Formula PD AG1343-35.2) is tabulated below.

Tablet Core	Quantity (mg)	w/w (%)
Nelfinavir mesylate,		
Calcium silicate		
Crospovidone		
Colloidal Silicon Dioxide, NF		
Magnesium stearate, NF		
Film Coating		
Total Target Weight/ Film coated tablet		100.0

What are the general clinical pharmacology characteristics of nelfinavir? (bioequivalence and exposure-response)

Bioequivalence

In both bioequivalence studies (healthy volunteers), the 625 mg tablet produced higher nelfinavir exposure than the 250 mg tablet following a single 1250 mg dose (Tables I and II).

Table I: Arithmetic Mean ± SD and Geometric LS Mean Ratios (90% CI) of Investigational 625 mg Nelfinavir Mesylate Tablets Relative to 250 mg Tablets (fasted)

	Arithmetic Mean ± SD		Geometric LSMean Ratio (90%CI)
Parameter (Units)	Treatment A: 5 x 250 mg VIRACEPT Tablets (N=27)	Treatment B: 2 x 625 mg Nelfinavir Mesylate Tablets (N=27)	Treatment B vs. Treatment A
AUC_∞ (µg*h/ml)	20.8 ± 13.2	25.8 ± 15.4	1.32 (1.11-1.57)
C_{max} (µg/ml)	2.73 ± 1.73	3.36 ± 1.74	1.24 (1.09-1.42)

Table II: Arithmetic Mean ± SD and Geometric LS Mean Ratios (90% CI) of Investigational 625 mg Nelfinavir Mesylate Tablets Relative to 250 mg Tablets (fed)

	Arithmetic Mean ± SD		Geometric LS Mean Ratio (90% CI)
Parameter (Units)	Treatment A: 5 x 250 mg VIRACEPT Tablets (N=28)	Treatment B: 2 x 625 mg Nelfinavir Mesylate Tablets (N=28)	Treatment B vs. Treatment A
AUC_∞ (µg*h/ml)	38.4 ± 14.1	46.2 ± 14.0	1.24 (1.16-1.33)
C_{max} (µg/ml)	4.89 ± 1.58	5.50 ± 1.48	1.15 (1.09-1.21)

Both BE studies were conducted with healthy volunteers who received a single 1250 mg NFV dose (5 x 250 mg tablets or 2 x 625 mg tablets) on two separate occasions. In the fasted BE study (712), both the C_{max} and AUC were outside the "no difference" boundary (80 – 125 %); whereas, in the fed BE study (713), C_{max} was within the boundary and AUC was not within the boundary.

Potentially the higher NFV exposure with the 625 mg tablet could lead to an increase in the incidence or severity of drug-related adverse events. The higher nelfinavir exposure is not expected to decrease NFV efficacy, based on exposure-response principles. The clinical

significance (safety) of the increased NFV exposure was evaluated in an exposure-response analysis conducted by the Pharmacometrics Reviewer, Dr. Jenny J. Zheng. The applicant also conducted an exposure-response analysis.

Exposure-Response Analyses

Both the applicant's and Pharmacometrics (PM) Reviewer's exposure-response analyses showed a relationship between NFV AUC and the incidence diarrhea. Other adverse events could not be adequately evaluated because of their low incidence rate. AUC was used as the exposure measure and diarrhea was used as the response measure. The choice of AUC as the exposure measure is reasonable to compare the formulations because AUC differed between the 625 and 250 mg tablet. Diarrhea is a suitable response measure because it is the most commonly reported nelfinavir-associated adverse event.

Study Populations

- Pooled Population 1

Pooled data were used in the exposure-response analyses (Applicant and Pharmacometrics Reviewer). These data (n = 317) were obtained from studies 503, 510, 511, and 542 in which patients had pharmacokinetic (exposure) and safety (response) data. Different dosage regimens were assessed in these studies including NFV 500 TID, 750 TID, 1000 TID and 1250 BID. Nelfinavir was given with other antiretroviral drugs in these clinical trials, but NFV exposure was not significantly altered by these drugs relative to when NFV was given alone.

- Pooled Population 2

Additional safety data were available from a clinical study in which delavirdine (DLV) and NFV were coadministered (Study 0073B). DLV inhibits NFV metabolism, increasing NFV exposure by 2- to 3-fold (see Extrinsic Factors: Drug-Drug Interactions) relative to when NFV is administered alone or with less potent inhibitors of NFV metabolism. Exposure data were unavailable in this study; however, NFV exposure could be assumed to be greater than that achieved with the 625 mg tablet or in Pooled Population 1 based on other PK study results (Studies 0073A, 0070 and 711).

Applicant's Exposure-Response Analyses

In the applicant's analyses, AUCs were stratified based on observations from previous clinical pharmacology studies. The AUC_{24hr} ranges were < 41, 41 –61 and > 61 μg·h/ml and corresponded to the lower quartile, interquartile range, and upper quartile of AUC values, respectively, observed in NFV clinical pharmacology studies (250 mg tablet). For the applicant's assessment, AUCs above 61 μg·h/ml correspond to high exposures, AUCs between 41 and 61 are the typical NFV exposures, and AUC < 41 are low exposures. The Statistical Reviewer (Dr. Susan Zhou) indicated that the distribution of AUCs using the above ranges was inconsistent with expected distribution theory (unequal numbers of patients in each quartile). The apparently inappropriate AUC stratification may have influenced the outcome of the applicant's exposure-response analyses. The PM Reviewer used a logistic regression approach that treated AUC as a continuous variable, rather than as a "categorical" variable defined by AUC range. The PM reviewer's data handling approach is more robust because fewer assumptions about data distribution are required.

Highlights from the applicant's exposure-response analyses (Pooled Populations 1 and 2) are as follows:

- Patients with drug-related diarrhea (≥ grade 2) had an increased incidence of diarrhea with increased plasma concentrations of NFV.
- There was no relationship between the incidence of nausea, flatulence, or rash with NFV exposure.
- There was no relationship between cardiac events (tachycardia most commonly reported) and nelfinavir exposure.
- There was no relationship between discontinuations due to adverse events and exposure to NFV.
- There were marked changes in hemoglobin and neutrophils in the high exposure group (AUC > 61) compared to the low exposure group; however, due to the small number of patients, the clinical significance of the observation is unclear.

The applicant's exposure-response conclusion was "exposure of nelfinavir above 61 μg·h/ml is not associated with new or unacceptable risks".

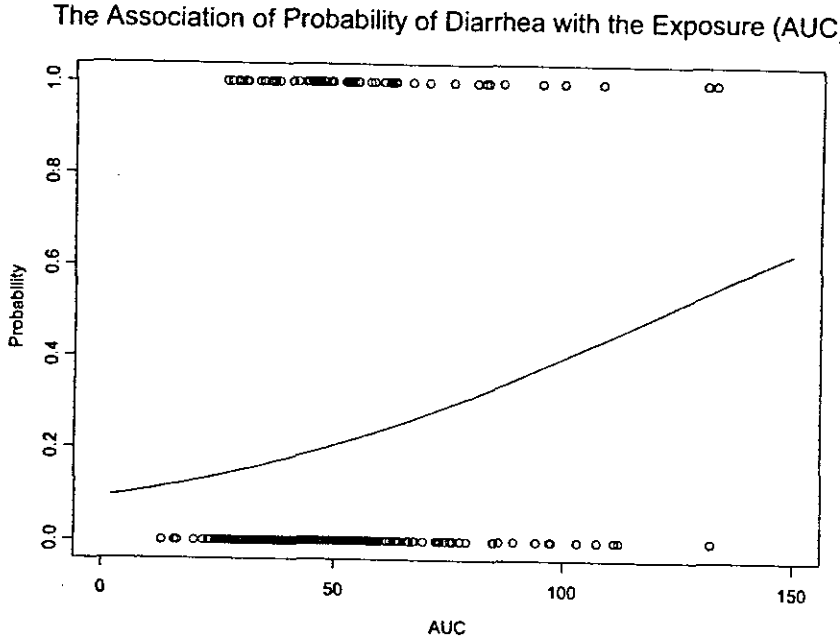
Reviewer's Note
Although the NFV-DLV produce higher NFV exposure than the 625 mg tablets, it is unclear if the NFV adverse event profile was changed in the presence of DLV.

The Pharmacometrics Reviewer generally agrees with the applicant's conclusions. However, the PM Reviewer used an alternative exposure-response analysis approach that provided a quantitative assessment of the difference in incidence of diarrhea for subjects taking the 250 mg tablet vs. the 625 mg tablet.

Pharmacometrics Review (PM Consult)
The main question addressed in the exposure-response analyses was "What is the clinical impact of the difference in exposure between the two nelfinavir tablet formulations"?

As indicated previously, the exposure (AUC)-response (diarrhea) data were fit to a logistic regression model; the PM review showed a statistically significant association between the probability of having diarrhea (≥ grade 2) and AUC_{24} ($p<0.0053$). The relationship between AUC and the probability of having diarrhea is depicted in figure 1.

Figure 1: Plot of Probability of Diarrhea vs. Nelfinavir AUC



Using the exposure-response information in conjunction with the AUC data from study 713 (fed BE study) the following predictions were made (Table III).

Table III: Mean (Range) Predicted probability of having diarrhea using Study 713 data

	250 mg tablet	625 mg tablet
AUC_{24}* in μg•hr/mL	76.78 (22.26-130)	92.5 (43.6-173.2)
Probability of having ≥ grade 2 diarrhea	0.31 (0.13-0.54)	0.37 (0.17-0.72)

* AUC_{24} was calculated as $2*AUC_{0-\infty}$, because $AUC_{0-\infty}$ was obtained from a single dose study.

Conclusions from the pharmacometrics analyses were:

1) An exposure-response relationship existed between the incidence of diarrhea and nelfinavir AUC.
2) Administration of the 625 mg tablet has a 6 % higher probability (based on mean values) of causing diarrhea (≥ grade 2) relative to the marketed 250 mg formulation.

Reviewer's Comment on Exposure-Response Findings

The finding of increased diarrhea with increased NFV exposure may be expected based on previous findings; in NDA 20-779, [redacted] the 1000 mg TID dose due to an unacceptable incidence of diarrhea in subjects. Taking the bioequivalence results into consideration, the following extrapolations can be made:

- 1000 mg TID via the 250 mg dose will give a total daily dose of 3000 mg and
- 1250 mg BID dose via the 625 mg tablet will be equivalent to a total daily dose of 3100 mg (24 % increase, based on AUC) or 2875 mg (15 % increase, based on C_{max}).

Clearly, the 625 mg tablets will provide a dose that was previously associated with unacceptable incidence of diarrhea. However, it should be noted that the applicant's definition of "unacceptable diarrhea" may have changed since the time of drug approval due

to improved understanding of NFV exposure-response relationships; this improved understanding also impacts the risk/benefit assessment.

Reviewer's Note: Potential Limitations of Exposure Response Analyses
Two major potential limitations of the exposure-response analyses are the fact that the data used for the prediction are from a limited number of subjects (n=28, Study 713) and that the AUC values may not be accurate. AUC data from a limited number of subjects may not be representative of the variability that has been observed in all NFV studies; some NFV PK studies with the 250 mg tablet had exposures that exceed those observed with the 625 mg tablet. Therefore, the apparent difference in exposure and subsequent difference in incidence of diarrhea may not always be valid. The accuracy of the AUC_{24} estimation is not certain, because 1) NFV exhibits diurnal variation, where morning trough concentrations are twice as high as evening trough concentrations (BID regimen) and 2) the analyses are based on extrapolation from non-steady data (single dose, rather than multiple dose data). It should be further noted that the pooled exposure-response data used in the analyses may have some shortcomings (e.g. unknown degree of patient compliance and uncertainty of adverse event reporting) associated with obtaining data from long-term clinical studies. In spite of the potential shortcomings, the exposure-response analysis is useful for estimating the clinical impact of increased NFV exposure (625 mg vs. 250 mg tablet).

Reviewers Recommendation
Based on the exposure-response relationship, there is an increased risk of diarrhea with the new 625 mg tablet formulation compared to the 250 mg marketed formulation. According to the applicant, diarrhea is a clinically manageable condition. The Medical Reviewer agrees with the applicant's assessment on the manageability of diarrhea. Therefore, the potential benefit of the new 625 mg tablet (lower pill burden) appears to outweigh the risk of increased occurrence of diarrhea. However, if necessary, patients can revert to using the 250 mg tablets if diarrhea is less tolerable with the 625 mg tablet compared to the 250 mg tablet. It should be noted that the applicant intends to continue marketing the 250 mg tablet.

Labeling (Based on Exposure-Response Analyses)
The risk-benefit implications of the 625 mg tablet relative to the marketed 250 mg tablet should be conveyed in the label. Wording has been included in the Adverse Events section of the proposed label (Clinical Division's proposal) and the Clinical Pharmacology section will state **See Adverse Events**.

What factors affect nelfinavir exposure?
The factors of formulation and metabolism (contribution of CYP3A and CYP2C19 pathways) affect nelfinavir exposure. The formulation factor was assessed in the bioequivalence studies and the metabolism factor was assessed in drug-drug interaction studies and via CYP2C19 genotyping and phenotyping.

Formulation

Nelfinavir exposure is affected by the extrinsic factor of formulation. The 625 mg tablet is not bioequivalent to the 250 mg tablet under both fasted and fed conditions; the AUC and C_{max} of the 625 mg tablet are higher than that of the 250 mg tablet [See What are the general clinical pharmacology characteristics of nelfinavir? (exposure-response)].

Drug-drug interactions

The drug-drug interaction studies included in this NDA indicate that NFV *in vivo* metabolism is mediated primarily via CYP3A and CYP2C19. Previous *in vitro* data (NDA 20-779) indicate that NFV is metabolized primarily by CYP3A (~50 %) and CYP2C19 (~33 %). The current label indicates that "*In vitro*, multiple cytochrome P-450 enzymes including CYP3A are responsible for metabolism of nelfinavir". In NDA 21-503 the applicant provided *in vivo* data from nelfinavir-delavirdine and nelfinavir-ritonavir drug interaction studies (Tables I – IV) that support the *in vitro* findings. Ritonavir (RTV) inhibits CYP3A and several other enzymes, whereas delavirdine (DLV) inhibits both CYP3A and CYP2C19. Coadministration of RTV with NFV (Kurowski *et al.*) resulted in a maximal 50 % increase in NFV exposure (Table I) and coadministration of NFV with DLV (Studies 0070, 0073 and 711) increased NFV exposure by ≥ 100 % (Tables II, III and IV). Collectively, data from these four studies indicate that DLV is a stronger metabolic inhibitor of NFV metabolism than RTV; consequently, CYP2C19 plays an important role in NFV metabolism. Consequently, the label should be updated to include the CYP2C19 information.

Table I: Nelfinavir-Ritonavir Interaction (n = 12, per group): Kurowski *et al*

PK Measure	Day 14		Day 31	
	NFV 1250 mg BID		NFV 1250 BID + RTV 100 mg	NFV 1250 BID + RTV 200 mg
	Group A	Group B	Group A	Group B
AUC_{0-12} (μg·hr/mL)	27.1 ± 6.8	30.8 ± 10.3	31.8 ± 9.3	36.9 ± 7.8
C_{max}(μg/mL)	3.39 ± 0.74	4.25 ± 1.65	4.09 ± 1.74	4.46 ± 0.78
C_{12} Morning(μg/mL)	1.76 ± 0.590	1.35 ± 0.563	1.71 ± 0.60	2.21 ± 0.80

Table II: Nelfinavir-delavirdine Interaction Study: M/3331/0070 (healthy volunteers)

	Group A		Group B
PK Measure	Day 7	Day 14	Day 14
	NFV alone 750 mg q 8 hr	NFV 750 mg q 8 hr + DLV 400 mg q 8 hr	NFV 750 mg q 8 hr + DLV 400 mg q 8 hr
C_{ss} in μg/mL (range)	3.2 ± 1.4	6.3 ± 1.4	6.7 ± 1.4
C_{max} in μg/mL (range)	4.2 ± 1.7	7.6 ± 1.4	8.1 ± 1.1
C_{min} in μg/mL (range)	2.2. ± 1.1	4.9 ± 1.4	5.3 ± 1.6

Table III: Nelfinavir-delavirdine Interaction Study: M/3331/0073 (HIV-infected subjects)

PK Measure	NFV 750 mg TID + DLV 400 mg TID	NFV 750 mg TID + DLV 600 mg TID
	N = 10	N = 10
AUC_{0-8} hr in μg/mL (range)	42.9 ± 9	48 ± 16
C_{max} in μg/mL (range)	6.6 ± 1.5	7.0 ± 2.1
C_{min} in μg/mL (range)	3.7 ± 1.0	3.9 ± 2.2

Table IV: Nelfinavir-delavirdine Interaction Study: Study 711

PK Measure	Day 14	Day 14
	NFV 1250 mg BID	NFV 1250 mg BID + DLV 600 mg BID
AUC_{0-24} in µg·hr/mL (range)	54.5	180
C_{max} in µg/mL (range)	3.75	9.64
$C_{predose}$ in µg/mL (range)	0.95	5.47

The drug-drug interaction information included in NDA 21-503 was not reviewed in detail because the information will not be included in the label and does not provide any dosing recommendations. It should be noted that the Viracept label has information from Study 0070 and a previously conducted NFV-RTV study. However, NFV-RTV information in the label was obtained under non-steady-state conditions; the information from the Kurowski study was obtained at steady-state conditions and may be more clinically relevant.

Additional Information Supporting the Role of CYP2C19 in Nelfinavir Metabolism

CYP2C19 genotyping information obtained from two subjects supports CYP2C19's role in NFV metabolism. CYP2C19 exhibits genetic polymorphism; approximately 2 % of the Caucasian population and 20 % of the Asian population are poor metabolizers. According to the applicant, the CYP2C19 poor metabolizers (based on CYP2C19 phenotype or genotype) have the following two characteristics: 1) NFV exposure is 2 to 3 fold higher than the median nelfinavir exposure (50 µg·h/ml) and 2) have little or no AG1402 (primary active NFV metabolite) in the plasma because AG1402 is generated exclusively by CYP2C19.

The data available for poor metabolizers are summarized in the table below.

Study	Metabolic Status	Regimen	AUC_{24}	AG1402
1131	Poor	1250 mg BID NFV + 10 mg atorvastatin for 2 weeks	155	Not indicated
521 *	Poor	750 mg NFV TID for 6 days	105	none
649 *	Poor	1250 mg NFV BID for 8 days	145	none

* same subject took part in both trials

The data from these two poor metabolizers support the claim that CYP2C19 plays a major role in the metabolism of nelfinavir.

What are the general biopharmaceutics characteristics of the 625 mg formulation (Bioequivalence, Food and Dissolution)?

Bioequivalence

As discussed previously, the new 625 mg tablet is not bioequivalent to the marketed 250 mg tablet. For additional bioequivalence information see "What are the general clinical pharmacology characteristics of nelfinavir? (bioequivalence and exposure-response)"

Food

Based on a cross-study comparison (Study 713 vs. 712), food increases NFV exposure by 2-3-fold. This food effect (increased NFV exposure) findings have been observed previously with the 250 mg tablet formulation. It is noted that the Viracept label indicates that

nelfinavir should be taken with food. The variability in PK in the fed state (< 40 %) is lower than in the fasted state (> 50 %).

Dissolution

Dissolution Method and Specification

The applicant provided sufficient dissolution information to select a dissolution method and to set a dissolution specification. Dissolution of the 625 mg tablet was evaluated under varying conditions (different media, paddle rotation speed and vessels). Based on evaluation of the dissolution data, the dissolution method and specification for the 625 mg tablet are:

- Dissolution Method

  USP Apparatus II (paddle)
  Dissolution medium 0.1 N HCl
  Paddle Speed 50 rpm
  Vessel Standard

Agreement was reached between the FDA and applicant on the dissolution method prior to NDA submission. This method is the same as that for the 250 mg tablet.

- Applicant's Proposed Specification Q = – % in 45 minutes

The proposed dissolution specification is unacceptable because — (mean) of NFV is dissolved within — (Table below). This reviewer recommends a specification of Q = — % in 45 minutes. This recommendation is more consistent with the dissolution data and the recommendations in the *Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms* than the applicant's proposed specification.

Dissolution data for the 625 mg tablets used in the bioequivalence studies are tabulated below*. See Appendix for Additional Dissolution data.

		Results	Results	Results
Test Name	**Acceptance Criteria**	**Lot DT2152R**	**Lot DT2153R**	**Lot DT2154R**
Dissolution	NLT / % (Q) in 45 min	% Dissolved	% Dissolved	% Dissolved
5 min				
10 min				
15 min				
20 min				
30 min				
45 min				
60 min				
90 min				

*Note: Previously reviewed dissolution data indicate that there is low variability in dissolution data for individual tablets (CV ____ at any given time point.

Overall, dissolution data for the 625 mg tablet (See Dr. George Lunn's Chemistry Review for Stability Information) indicate that the 625 mg tablet will meet the S1 criterion for Q = – % in 45 minutes and meet the S2 criterion for Q = — % in 45. Thus, the specification, Q = — % at 45 minutes is reasonable in this reviewer's opinion.

Dissolution Data Supporting Dispersion of Tablets (Dosage and Administration Section)
Based on the dissolution data below (see Appendix for more detailed data), dispersed (dissolved) tablets are expected to perform in a similar manner (meet dissolution specification) as intact tablets. Therefore, patients unable to swallow tablets may dissolve 625 mg tablets in a small volume of water and consume liquid. Similar dissolution data were provided to support dispersion of the 250 mg tablets (NDA 20779 SLR 010) for patients unable to swallow tablets.

Mean ± SD (CV %) Dissolution Data for Whole Nelfinavir mesylate 625 mg tablets and Dispersed Nelfinavir Tablets (lot # DT21532)

	% of nelfinavir mesylate dissolved							
Time (min)	5	10	15	20	30	45	60	90
Whole Tablets	43.82 ± 1.80 (4.1)	63.10 ± 2.14 (3.4)	71.93 ± 2.59 (3.6)	77.19 ± 2.69 (3.5)	83.29 ± 2.77 (3.3)	88.08 ± 2.82 (3.2)	90.78 ± 2.89 (3.2)	93.47 ± 2.99 (3.2)
Dispersed Tablets	68.16 ± 2.77 (4.1)	77.45 ± 2.43 (3.1)	81.89 ± 2.27 (2.8)	84.64 ± 2.14 (2.5)	87.87 ± 1.93 (2.2)	90.66 ± 1.79 (2.0)	92.30 ± 1.61 (1.7)	94.09 ± 1.45 (1.5)

V. Labeling

Summary of Applicant's Proposed Labeling Changes

1. Description of new 625 mg tablet
2. Clinical Pharmacology Section
- Included statement about absence of absolute bioavailability data
- Provided bioequivalence information (625 mg tablet compared to 250 mg tablet)
- Included information about the contribution of CYP2C19 to nelfinavir metabolism
3. Warning Section (Drug Interactions)
- Included information about CYP2C19's contribution to nelfinavir metabolism
- Modified list of drugs that are not expected to undergo clinically significant metabolically-based drug interactions (removed ——

4. Dosage and Administration Section
- Included 625 mg tablet as a Viracept formulation, indicating that the 625 mg tablet could be dissolved in water for patients unable to swallow whole tablets.

OCPB Labeling Recommendations: Labeling Revisions to Proposed Labeling Changes
In general, the applicant's labeling comments are acceptable. The following comments and revisions were conveyed to the applicant on March 28, 2003.

1. Clinical Pharmacology
- Comments: applicant was asked to put pharmacokinetic data in a tabular format, add AUC_{0-24} or C_{ssavg} data, and replace the +/- sign with ± sign.
- Deleted ——————————
- Reworded bioequivalence information to reflect findings from bioequivalence (fasted conditions) and relative bioavailability assessments; additionally, applicant asked to include bioavailability information on approved powder formulation
- Included see Adverse Events statement.
- The word —— was replaced with enzyme

- *In vitro* metabolism section reordered.

2. Warnings
- Deleted [redacted]
- Included information about potential QT_c prolongation (inserted by clinical division) by NFV's inhibition on CYP3A metabolism of other drugs.

3. Precautions (Drug interactions)
- Changed list of drugs that are unlikely to undergo clinically significant drug-drug interactions (deleted [redacted]

Note: Labeling Update
The applicant accepted all of the OCPB labeling recommendations. The final approved label will incorporate the described labeling changes.

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APPENDIX

Study 713: Fed BE Study
Study 712: Fasted BE Study
Dissolution Data
Pharmacometrics Review

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Study Title: A Randomized, Phase I, Open-label, Crossover Study to Assess the Bioequivalence of 250-mg \ And 625-mg Tablets of Nelfinavir Mesylate Under the Fed Condition (Study 713).
Investigator: ———
Study Center: ———
Study period: 10/2001

Objective:
To determine the bioequivalence of the currently marketed 250-mg VIRACEPT tablets (United States) and the 625-mg tablet formulation of nelfinavir mesylate under fed conditions.

Study design:
This was a single-dose, randomized, open-label, 2-way crossover study. Twenty-eight subjects (healthy volunteers) were randomly assigned to receive either treatment A or treatment B (described below) at the first dosing and the alternative regimen at the second dosing, under fed conditions. There was a 2- to 7-day washout period between treatments. The treatments were as follows:

- Treatment A (reference): A single 1250 mg dose of nelfinavir mesylate, consisting of five 250 mg VIRACEPT tablets
- Treatment B (test): A single 1250 mg dose of nelfinavir mesylate, consisting of two 625 mg nelfinavir mesylate tablets

Treatments A and B were administered in the morning 5 to 10 minutes after the subject completed a standard light breakfast (286 kcal, 1.1 g fat).

Formulation:
- Test formulation: nelfinavir mesylate 625 mg tablet; lot number DT21521.
- Reference formulation: nelfinavir mesylate 250 mg tablet; lot number YT21451A.

Blood Samples
Blood samples were collected before each dose and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, and 24 hours after each dose.

Bioanalytical Assay
Plasma concentrations of nelfinavir (NFV) were measured by a validated HPLC method with UV detection. The assay performance was acceptable. The interassay coefficients of variation of the quality controls for the analytical runs ranged from — . . ., with percentage differences from the theoretical concentration ranging from — The assay concentration range was — µg/mL. Inspection of sample chromatograms indicates that the assay was specific for nelfinavir. Coefficients of correlation for individual runs were greater than —

Pharmacokinetics (PK)
The following NFV PK measures were determined: $AUC_{0-\infty}$, AUC_{last}, C_{max}, t_{max}, and $t_{1/2}$ were estimated for both treatments using SAS, version 6.12.

Pharmacokinetic Analysis
Standard pharmacokinetic-statistical analyses were used to evaluate bioequivalence of the 625 mg formulation (250 mg as reference formulation).

Results:
All 28 subjects received at least one dose of study drug and completed the study. There was no significant difference among the treatment groups with respect to age, sex, or race (Table I).

Demographic Variable	Value
Age (years)	
Mean (SD)	32 (10.6)
Range	18-55
Sex, N (%)	
Men	10 (36)
Women	18 (64)
Race a N (%)	
White	21 (75)
Black	1 (4)
Asian	1 (4)
Hispanic	5 (18)
Height (in)	
Mean (SD)	68.4 (3.7)
Range	63 - 77
Weight (lb)	
Mean (SD)	155.0 (25.5)
Range	107 - 223

The 625 mg tablet formulation was not bioequivalent to the marketed 250 mg tablet formulation (Table II). For most subjects (n = 25, increased NFV exposure vs. n = 3, decreased NFV exposure; see Appendix for individual data) receiving the 1250 mg single dose, the NFV exposure for the 625 mg tablets was greater than for the 250 mg tablets. The clinical significance of the increased exposure was evaluated in the Pharmacometrics Review.

Table II: Geometric Least Squares Mean* (95% CI) and Geometric LS Mean Ratios (90% CI) of Investigational 625 mg Nelfinavir Mesylate Tablets Relative to 250 mg Tablets (1250 mg single dose, n =28)

	Geometric LS Mean (95% CI)		Geometric LS Mean Ratio (90% CI)
Parameter (units)	Treatment A: 250 mg VIRACEPT Tablets	Treatment B: 625 mg Nelfinavir Mesylate Tablets	Treatment B vs. Treatment A
$AUX_{0-\infty}$ (µg*h/mL)	35.7 (33.6-37.8)	44.2 (41.7-46.9)	1.24 (1.16-1.33)
AUC_{last} (µg*h/mL)	34.9 (33.0-37.0)	43.4 (41.0-46.0)	1.24 (1.16-1.33)
C_{max} (µg/mL)	4.62 (4.41-4.84)	5.31 (5.06-5.56)	1.15(1.09-1.21)

* See Appendix for additional PK data listings

Comment on Variability
The coefficients of variability (CVs) for the exposure measures were less than 40 % (range 27 – 37 %). These CV values are comparable to those observed in other studies where subjects received nelfinavir in the fed state.

Safety Highlights from Applicant's Summary:
Four (14%) of the 28 subjects experienced 12 treatment-emergent adverse events (AEs), seven of which were determined by the investigator to be related to the study drug. No death, serious AE, or discontinuation due to an AE occurred among subjects participating in this study.

Conclusion:
When administered as a single 1250 mg single dose, the 625-mg formulation was not bioequivalent to the marketed 250 mg tablets; the 625 mg tablet produces 24 % and 15 % higher nelfinavir AUC and C_{max}, respectively than the 250 mg tablet.

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Appendix

Pharmacokinetic Data for Study 713

NELFINAVIR AUC[INF] (ug.H/mL)

SUBJECT #	625-MG NFV	250-MG NFV	DIFFERENCE	% DIFF.	RATIO
1			3.3	6.6	1.07
2			11.2	31.3	1.31
3			-8.1	-14.8	0.85
4			10.5	17.8	1.18
5			-6.8	-10.4	0.90
6			9.3	27.2	1.27
7			14.4	44.0	1.44
8			10.6	23.7	1.24
9			13.6	63.0	1.63
10			6.7	17.7	1.18
11			3.0	9.3	1.09
12			7.1	21.2	1.21
13			8.8	41.0	1.41
14			7.8	13.4	1.13
15			7.7	19.7	1.20
16			7.2	21.5	1.22
17			0.2	0.5	1.00
18			22.5	35.0	1.35
19			2.5	4.6	1.05
20			12.6	113.6	2.14
21			19.3	61.6	1.62
22			26.7	101.1	2.01
23			5.1	14.9	1.15
24			-4.5	-11.0	0.89
25			5.2	16.7	1.17
26			14.0	37.1	1.37
27			2.4	12.1	1.12
28			7.6	36.3	1.36
N					
GEOMETRIC LS MEAN	44.2	35.7			
95% CI UPPER	46.9	37.8			
95% CI LOWER	41.7	33.6			
GEOMETRIC MEAN	44.2	35.7			
MEAN OF LOGS	3.79	3.57			
SD OF LOGS	0.31	0.41			
ARITHMETIC MEAN	46.2	38.4	7.9	27.0	1.27
SD	14.9	14.1	7.9	29.6	0.30
CV %	30	37	100	110	23
MEDIAN	46.9	35.1	7.7	20.4	1.20
MINIMUM			-8.1	-14.8	0.85
MAXIMUM			26.7	113.6	2.14

GEOM. LS MEAN RATIO	1.24				
90% CI UPPER	1.33				
90% CI LOWER	1.16				
ANOVA P-VALUE	0.0001				

NFV=VIRACEPT 2 X 650-MG OR 5 X 250-MG ; DIFF=DIFFERENCE, LS=LEAST-SQUARES
SD=STANDARD DEVIATION, GEOM=GEOMETRIC; CV=COEFFICIENT OF VARIATION, CI=CONFIDENCE INTERVAL

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NELFINAVIR CMAX (ug/mL)

SUBJECT #	625-MG NFV	250-MG NFV	DIFFERENCE	% DIFF.	RATIO
1			-0.52	-23.4	0.77
2			-2.32	-65.2	0.35
3			0.51	18.7	1.19
4			0.43	8.4	1.08
5			0.20	37.1	1.37
6			0.08	2.4	1.02
7			0.60	14.1	1.14
8			1.04	37.7	1.38
9			0.45	26.0	1.28
10			1.69	61.9	1.62
11			1.26	48.3	1.48
12			0.26	7.9	1.08
13			0.20	7.5	1.08
14			3.20	87.7	1.88
15			0.17	3.9	1.04
16			1.48	77.5	1.77
17			-0.57	-17.2	0.83
18			1.41	21.4	1.21
19			3.14	118.5	2.18
20			0.21	28.7	1.29
21			-0.55	-18.5	0.81
22			0.94	145.4	2.45
23			1.30	113.0	2.13
24			-0.08	-2.6	0.97
25			0.88	50.9	1.51
26			1.00	47.8	1.48
27			0.75	52.8	1.53
N					
GEOMETRIC LS MEAN	2.91	2.34			
95% CI UPPER	3.25	2.61			
95% CI LOWER	2.60	2.09			
GEOMETRIC MEAN	2.93	2.35			
MEAN OF LOGS	1.07	0.85			
SD OF LOGS	0.57	0.61			
ARITHMETIC MEAN	3.35	2.73	0.64	33.1	1.33
SD	1.74	1.37	1.10	46.8	0.47
CV %	52	50	173	142	35
MEDIAN	3.03	2.73	0.51	28.0	1.28
MINIMUM			-2.32	-65.2	0.35
MAXIMUM			3.20	145.4	2.45

GEOM. LS MEAN RATIO	1.24				
90% CI UPPER	1.42				
90% CI LOWER	1.09				
ANOVA P-VALUE	0.0087				

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Study Title: A Randomized, Phase I, Open-label, Crossover Study to Assess the Bioequivalence of 250-mg and 625-mg Tablets of Nelfinavir Mesylate Under the Fasting Condition (Study 712)

Investigator: ———

Study center: ———

Study period: 09/01

Objective:

To determine the bioequivalence of the currently marketed 250-mg VIRACEPT tablets (United States) and the 625-mg tablet formulation of nelfinavir mesylate under fasting conditions.

Study design:

This was a phase I, single-dose, randomized, open label, 2-way crossover, single-center study. Twenty-eight subjects (healthy volunteers) were randomly assigned to receive either treatment A or treatment B (described below) at the first dosing and the alternative regimen at the second dosing, under fasting conditions. There was a 2- to 7-day washout period between treatments. The treatments were as follows:

- Treatment A (reference): A single 1250 mg dose of nelfinavir mesylate, consisting of five 250 mg VIRACEPT tablets
- Treatment B (test): A single 1250 mg dose of nelfinavir mesylate, consisting of two 625 mg nelfinavir mesylate tablets

Treatments A and B were administered after an overnight fast of at least 10 hours.

Formulations:

- Test formulation: nelfinavir mesylate 625 mg tablet; lot number DT21521
- Reference formulation: nelfinavir mesylate 250 mg tablet; lot number YT21451A.

Blood Samples

Blood samples were collected before each dose and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, and 24 hours after each dose.

Bioanalytical Assay

Plasma concentrations of nelfinavir (NFV) were measured by a validated HPLC method with UV detection. The assay performance was acceptable. The interassay coefficients of variation of the quality controls for the analytical runs ranged from — with percentage differences from the theoretical concentration ranging from — The assay concentration range was — μg/mL. Inspection of sample chromatograms indicates that the assay was specific for nelfinavir. Coefficients of correlation for individual runs were greater thar —

Pharmacokinetics (PK)

The following NFV PK measures were determined: $AUC_{0-\infty}$, AUC_{last}, C_{max}, t_{max}, and $t_{1/2}$ were estimated for both treatments using SAS, version 6.12.

Pharmacokinetic Analysis

Standard pharmacokinetic-statistical analyses were used to evaluate bioequivalence of the 625 mg formulation (250 mg as reference formulation).

Results

Twenty-eight subjects received at least one dose of study drug and 27 subjects completed the study. Subject demographics are summarized in Table I.

Table I: Subject Demographics

Demographic Variable	Value
Age (years)	
Mean (SD)	33.3 (11.3)
Range	18-55
Sex N (%)	
Men	10 (37)
Women	17 (63)
Race N (%)	
Caucasian	21 (78)
Black	1 (4)
Asian	1 (4)
Hispanic	4 (15)
Height (in)	
Mean (SD)	68.5 (3.7)
Range	63-77
Weight (lb)	
Mean (SD)	153.6 (23.5)
Range	107-223

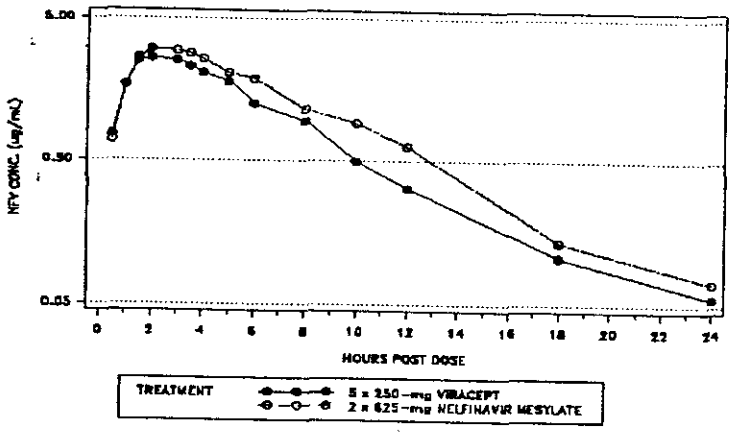
N = number, SD = standard deviation.

There was no significant difference between the treatment groups with respect to age, sex, or race. According to the applicant, one subject (# 28) was discontinued from participation in this study due to mild abdominal cramping, nausea, and lightheadedness; this subject also experienced vomiting but was not withdrawn because of that adverse event.

Pharmacokinetic results:

The plasma concentration-time profiles (median) for subjects receiving a single 1250 mg dose (250 mg tablet or 625 mg tablet) of nelfinavir are depicted in figure 1.

Figure 1: Nelfinavir plasma concentration-time profile (median)



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The 625 mg formulation was not bioequivalent to the marketed 250 mg formulation, as shown in Table II.

Table II: Geometric Least Squares Mean* (95% CI) and Geometric LS Mean Ratios (90% CI) of Investigational 625 mg Nelfinavir Mesylate Tablets Relative to 250 mg Tablets (1250 mg single dose, n =27)

	Geometric LS Mean (95% CI)		Geometric LSMean Ratio (90%CI)
Parameter (Units)	Treatment A: 250 mg VIRACEPT Tablets	Treatment B: 625 mg NFV Mesylate Tablets	Treatment B vs. Treatment A
$AUC_{0-\infty}$ (µg*h/mL)	16.2 (14.0-18.7)	21.4 (18.5-24.8)	1.32 (1.11-1.57)
AUC_{last}(µg*h/mL)	15.5(13.3-18.0)	20.8(17.9-24.2)	1.34(1.12-1.60)
C_{max} (µg/mL)	2.34(2.09-2.61)	2.91(2.60-3.25)	1.24(1.09-1.42)

*See Appendix for additional PK data listings

The exposure achieved with the 625 mg formulation was greater than that of the marketed reference 250 mg tablets. For most subjects (n = 21, increased NFV exposure vs. n = 6, decreased NFV exposure; see Appendix for individual data) receiving the 1250 mg single dose, the NFV exposure for the 625 mg tablets was greater than for the 250 mg tablets. The clinical significance of the increased exposure was evaluated in the Pharmacometrics Review.

Comment on Variability

The coefficients of variability (CVs) for the exposure measures were between 50% and 65%. These CV values are higher than the 30% to 40% variability observed in other studies of VIRACEPT administered to subjects in the fed condition (e.g. Study 713). These results indicate that the variability of NFV is greater in the fasting than in the fed condition.

Safety Highlights from Applicant's Summary

Eight (29%) of the 28 subjects experienced at least one treatment-emergent adverse event (AE), determined by the investigator to be related to the study drug. All of the AEs were graded as mild in severity, except one instance of vomiting, graded as moderate in severity. The most frequently reported treatment-related AEs were abdominal pain and diarrhea. No death or serious AE occurred among subjects participating in this study.

Conclusion

Following a single 1250 mg dose, the 625 mg formulation was not bioequivalent to the marketed 250 mg tablets; the 625 mg tablet produces 32 % and 24 % higher nelfinavir AUC and C_{max}, respectively, than the 250 mg tablet.

Appendix

Pharmacokinetic Data for Study 712

NELFINAVIR AUC[INF] (ug.H/mL)

SUBJECT #	625-MG NFV	250-MG NFV	DIFFERENCE	% DIFF.	RATIO
1			1.2	11.5	1.12
2			-23.3	-73.8	0.26
3			1.6	6.4	1.06
4			7.0	17.7	1.18
5			1.0	36.5	1.37
6			0.7	2.7	1.03
7			-2.3	-6.5	0.93
8			10.9	59.3	1.59
9			4.8	43.2	1.43
10			11.5	54.9	1.55
11			13.3	80.9	1.81
12			5.6	31.0	1.31
13			1.7	11.2	1.11
14			28.4	102.7	2.03
15			-1.5	-4.4	0.96
16			16.4	134.6	2.35
17			14.7	-36.1	0.64
18			12.7	21.8	1.22
19			25.8	112.6	2.13
20			3.5	90.6	1.91
21			-5.7	-24.7	0.75
22			6.8	212.8	3.13
23			10.1	198.6	2.99
24			-5.0	-19.6	0.80
25			8.3	98.1	1.98
26			6.5	42.0	1.42
27			5.8	88.2	1.88
N					
GEOMETRIC LS MEAN	21.4	16.2			
95% CI UPPER	24.8	18.7			
95% CI LOWER	18.5	14.0			
GEOMETRIC MEAN	21.6	16.3			
MEAN OF LOGS	3.07	2.79			
SD OF LOGS	0.65	0.79			
ARITHMETIC MEAN	25.8	20.8	5.0	47.9	1.48
SD	15.4	13.2	10.7	67.3	0.67
CV %	60	64	213	141	46
MEDIAN	23.6	18.5	5.6	36.5	1.37
MINIMUM			-23.3	-73.8	0.26
MAXIMUM			28.4	212.8	3.13

GEOM. LS MEAN RATIO	1.32				
90% CI UPPER	1.57				
90% CI LOWER	1.11				
ANOVA P-VALUE	0.0102				

NFV=VIRACEPT 3 X 650-MG OR 5 X 250-MG ; DIFF=DIFFERENCE; LS=LEAST-SQUARES
SD=STANDARD DEVIATION; GEOM=GEOMETRIC; CV=COEFFICIENT OF VARIATION; CI=CONFIDENCE INTERVAL

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NELFINAVIR CMAX (ug/mL)

SUBJECT #	625-MG NFV	250-MG NFV	DIFFERENCE	% DIFF.	RATIO
1			-0.52	-23.4	0.77
2			-2.32	-65.2	0.35
3			0.51	18.7	1.19
4			0.43	8.4	1.08
5			0.20	37.1	1.37
6			0.08	2.4	1.02
7			0.60	14.1	1.14
8			1.04	37.7	1.38
9			0.45	26.0	1.28
10			1.69	61.9	1.62
11			1.26	48.3	1.48
12			0.26	7.9	1.08
13			0.20	7.5	1.08
14			3.20	87.7	1.88
15			0.17	3.9	1.04
16			1.48	77.5	1.77
17			-0.57	-17.2	0.83
18			1.41	21.4	1.21
19			3.14	118.5	2.18
20			0.21	28.7	1.29
21			-0.55	-18.5	0.81
22			0.94	145.4	2.45
23			1.30	113.0	2.13
24			-0.08	-2.6	0.97
25			0.88	50.9	1.51
26			1.00	47.8	1.48
27			0.75	52.8	1.53
N					
GEOMETRIC LS MEAN	2.91	2.34			
95% CI UPPER	3.25	2.61			
95% CI LOWER	2.60	2.09			
GEOMETRIC MEAN	2.93	2.35			
MEAN OF LOGS	1.07	0.85			
SD OF LOGS	0.57	0.61			
ARITHMETIC MEAN	3.35	2.73	0.64	33.1	1.33
SD	1.74	1.37	1.10	46.8	0.47
CV %	52	50	173	142	35
MEDIAN	3.03	2.73	0.51	28.0	1.28
MINIMUM			-2.32	-65.2	0.35
MAXIMUM			3.20	145.4	2.45

GEOM. LS MEAN RATIO	1.24				
90% CI UPPER	1.42				
90% CI LOWER	1.09				
ANOVA P-VALUE	0.0087				

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Dissolution Data

Dissolution Profiles for VIRACEPT Tablets, 250 mg Lot YT21451 and Nelfinavir Mesylate Tablets, 625 mg Lot DT21521 Are Provided Below.

Time Point	VIRACEPT Tablets, 250 mg Lot YT21451		Nelfinavir Mesylate Tablets, 625 mg Lot DT21521	
Minutes	% Dissolved	SD	% Dissolved	SD
5		3.0		2.2
10		3.5		3.6
15		3.0		3.0
20		2.1		2.0
30		1.3		1.3
45		1.1		0.9
60		1.0		0.9
90		0.9		0.8

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Table 8. Comparative Dissolution Profiles for Tablet Lots used in the Bioequivalence Study

	Percent Recovery of Nelfinavir Mesylate															
Time Pull	5 minutes		10 minutes		15 minutes		20 minutes		30 minutes		45 minutes		60 minutes		90 minutes	
Lot DT2152R 625 mg	Mean SD	35 2.2	Mean SD	53 3.6	Mean SD	63 3.0	Mean SD	70 2.0	Mean SD	79 1.3	Mean SD	86 0.9	Mean SD	90 0.9	Mean SD	93 0.8
Lot YT21451A 250 mg	Mean SD	52 3.0	Mean SD	70 3.5	Mean SD	79 3.0	Mean SD	84 2.1	Mean SD	89 1.3	Mean SD	92 1.1	Mean SD	94 1.0	Mean SD	96 0.9

Table 7. Dissolution Results for the Nelfinavir Mesylate 625 mg Tablets - NDA Registrational Batches

	Percent Recovery of Nelfinavir Mesylate							
Time Pull	*5 minutes*	*10 minutes*	*15 minutes*	*20 minutes*	*30 minutes*	*45 minutes*	*60 minutes*	*90 minutes*
Lot DT2152R	Mean 35 SD 2.2	Mean 53 SD 3.6	Mean 63 SD 3.0	Mean 70 SD 2.0	Mean 79 SD 1.3	Mean 86 SD 0.9	Mean 90 SD 0.9	Mean 93 SD 0.8
Lot *DT2153R*	Mean 35 SD 2.3	Mean 56 SD 2.5	Mean 67 SD 2.4	Mean 74 SD 2.6	Mean 82 SD 2.5	Mean 88 SD 2.4	Mean 92 SD 2.3	Mean 95 SD 2.1
Lot DT2154R	Mean 28 SD 1.2	Mean 43 SD 3.3	Mean 55 SD 2.4	Mean 64 SD 1.3	Mean 75 SD 1.4	Mean 83 SD 1.8	Mean 87 SD 2.0	Mean 91 SD 2.3

The dissolution profiles for Whole Nelfinavir Mesylate 625 mg film coated tablets, lot# DT21532.

Sample ID	% Dissolution							
	5 min.	10 min.	15 min.	20 min.	30 min.	45 min.	60 min.	90 min.
DT21532 V1								
DT21532 V2								
DT21532 V3								
DT21532 V4								
DT21532 V5								
DT21532 V6								
Average	43.82	63.10	71.93	77.19	83.29	88.08	90.78	93.47
SD	1.80	2.14	2.59	2.69	2.77	2.82	2.89	2.99
%RSD	4.1	3.4	3.6	3.5	3.3	3.2	3.2	3.2

The dissolution profiles for Dispersed Nelfinavir Mesylate 625 mg film coated tablets, lot# DT21532.

Sample ID	% Dissolution							
	5 min.	10 min.	15 min.	20 min.	30 min.	45 min.	60 min.	90 min.
DT21532 V1								
DT21532 V2								
DT21532 V3								
DT21532 V4								
DT21532 V5								
DT21532 V6								
Average	68.16	77.45	81.89	84.64	87.87	90.66	92.30	94.09
SD	2.77	2.43	2.27	2.14	1.93	1.79	1.61	1.45
%RSD	4.1	3.1	2.8	2.5	2.2	2.0	1.7	1.5

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-503
Submission date:	July 1, 2002
Product:	625 mg tablet
Brand name:	Viracept
Generic name:	nelfinavir mesylate
Sponsor:	Pfizer
Type of submission:	PM consult
Primary Reviewer:	Robert Kumi, Ph.D.
PM reviewer:	Jenny J Zheng, Ph.D.

SUMMARY:

VIRACEPT ™ (nelfinavir mesylate) is approved for the treatment of HIV infection. The recommended adult dose for VIRACEPT is 1250 mg twice daily (eg, 5 x 250 mg tablets BID) or 750 mg 3 times daily (3 x 250 mg tablets TID) in combination with nucleoside analogues. To reduce pill burden and increase compliance in HIV-infected patients, a higher strength tablet of 625 mg nelfinavir mesylate was developed. However, the bioequivalence studies showed that the new formulation, 625 mg tablet, is not bioequivalent to the current marketed formulation, 250 mg tablet. The area under the curve (AUC) increased 24% and 33% with the 625 mg tablet under fed and fasted conditions, respectively. Due to the moderate increased exposure for the new formulation as compared with the current formulation, the safety of higher exposure due to the new formulation was assessed retrospectively using data from 6 studies. The six studies used the marketed 250 mg tablet.

The daily exposure (AUC_{24}) and the safety data were pooled from 4 studies. Total of 317 subjects were included. According to the AUC_{24} values, the individuals were grouped in low exposure (AUC24<41 mg•h/L), typical exposure (AUC24: 41-61mg•h/L) and high exposure groups (AUC24>61 mg•h/L). The general adverse events such as diarrhea, nausea, rash, and flatulence, cardiac effects, and the laboratory values were compared between the three exposure groups. It appeared that the incidence of drug related diarrhea was higher in high exposure group. No clear trend was seen for the other adverse effects with regard to exposure. The sponsor concluded that diarrhea is a manageable adverse event therefore the higher exposure for the new formulation would not result in a significant safety concern.

The safety data from two phase 3 trials were also used to support the safety of the new formulation. In the two phase 3 trials, nelfinavir was co-administered with delavirdine and other drugs. The pharmacokinetic studies suggested that co-administration of delavirdine with nelfinavir would increase nelfinavir exposure by 2-3 fold. Therefore, the exposure of nelfinavir in these two phase 3 trials would be higher than the nelfinavir exposure observed for the new formulation. Therefore, the moderate increase in exposure for the new formulation should be acceptable if the safety profile from the two phase 3 trials were acceptable. The safety assessment of the two phase 3 trials (n=130) showed that the adverse events of diarrhea, nausea, flatulence, rash, and asthenia were not exacerbated by increased exposure. In addition, no new adverse events appeared outside the safety profile expected for VIRACEPT.

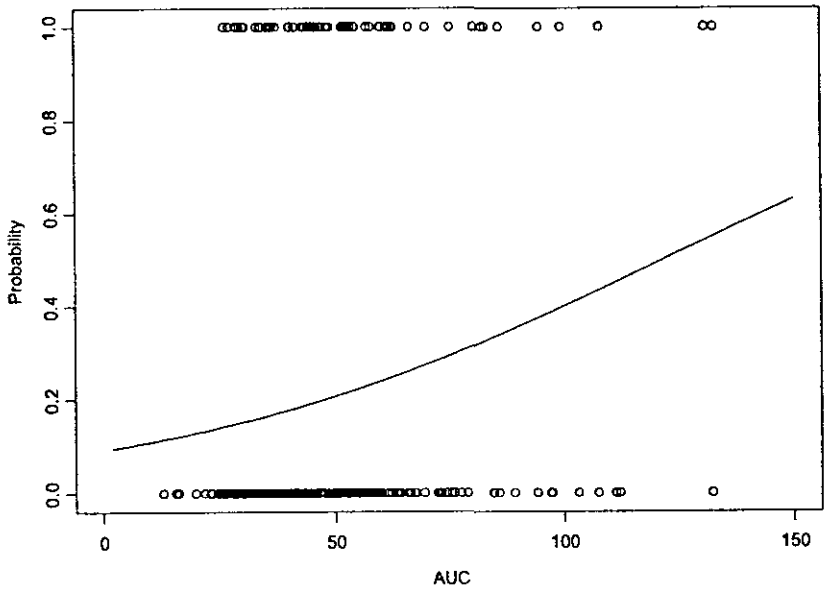
In summary, the sponsor concluded that the safety of the new formulation should not be a concern even though a moderate increase in nelfinavir exposure was observed for the new formulation for the reasons as follows:

1) Only the incidence of diarrhea was higher at high exposure group, but diarrhea was considered to be manageable event.
2) No new adverse events were seen in the two phase 3 trials in which the exposure was believed to be higher as compared with the exposure observed with the new formulation when nelfinavir was used ALONE.

The sponsor's assessment was focused on the new formulation and no safety comparison was made between the two formulations. Clinical assessment is needed to decide if the diarrhea is manageable event and the database from two trials which include 130 subjects were sufficient to make safety assessment for the higher exposure. However, in this reviewer's opinion, it is important to make a safety comparison between the new formulations and to quantify the difference in safety attributed by the different exposures between two formulations.

An exposure response relationship was established using pooled data from the four phase 2/3 studies. Since diarrhea is the most common adverse event and more diarrhea event was observed in the higher exposure group, a logistic regression analysis was conducted for the exposure response relationship. A statistically significant association was found between the probability of having nelfinavir related grade 2 or above diarrhea and the daily AUC (AUC_{24}) ($p<0.0053$). The relationship is presented in the Figure below.

The Association of Probability of Diarrhea with the Exposure (AUC)



Based on bid regimen, the daily exposure from bioequivalence study under fed condition was calculated as $2*AUC_{0-\infty}$ which was obtained from a single dose study. Using relationship described in Figure 1 and the daily exposures, the probability of having diarrhea for the two formulations was calculated and shown in the following table. The results showed that a higher probability of having diarrhea is associated with the new formulation. The mean probability of having diarrhea is 37% and 31% for new and current marketed formulation, respectively. Thus, the increase is only 6%.

The predicted probability of having diarrhea for Study 713

		250 mg tablet	625 mg tablet
AUC_{24} (mg/h•L)*	Mean	76.78	92.5
	Min-Max	22.26-130	43.6-173.2
Probability of having diarrhea	Mean	0.31	0.37
	Min-Max	0.13-0.54	0.17-0.72

*: Based on the bid regimen, AUC_{24} was calculated as $2*AUC_{0-}$ which was obtained from a single dose study.

In conclusion, 1) This analysis demonstrated that the exposure response relationship can be used to quantitatively compare the adverse event of interest between two formulations when the two formulations are not bioequivalent; 2) It shows that a higher probability of having diarrhea is associated with the use of new formulation; and 3) Using the new formulation, the increase of incidence of having diarrhea would be increased by 6% as compared to the current marketed formulation.

COMMENTS:

1. The safety comparison between the two formulations was focused on only diarrhea. Since the incidence of having other adverse event was lower, no relationship could be found between the other adverse event and the exposure.
2. The relationship between rash and exposure was examined; there is no association between rash and exposure.
3. The sponsor used the data from two phase 3 trials in which nelfinavir was used with delavirdine and the other drugs to support the safety of new formulation because a higher nelfinavir exposure was expected in these two trials. It needs to be pointed out that the two trials can be used to support the safety of the new formulation when new formulation is used without a metabolic inhibitor. The exposure would be higher when new formulation is co-administered with delavirdine as compared with the exposures in these two trials. Therefore, no safety data support the use of the new formulation with delavirdine.
4. This analysis was focused on the comparison between marketed and the new formulation. A caution needs to be taken when interpreting the absolute probability of diarrhea for each formulation. The exposures used for predicting the probability of diarrhea for the new formulation was obtained after the single dose in phase 1 study but the exposures used in exposure response relationship was obtained after multiple doses in phase 3 studies.

RECOMMENDATION:

The effect of moderate increase in nelfinavir exposure for the 625 mg tablet might be acceptable. Using diarrhea as the adverse event marker, exposure response analysis shows that a higher probability of having diarrhea is associated with the use of the new formulation. However, the increased incidence of having diarrhea by using the new formulation was only 6% as compared to using the current marketed formulation.

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VIRACEPT ™ (nelfinavir mesylate), a potent and specific inhibitor of HIV protease received accelerated approval for the treatment of HIV infection in the United States in March of 1997.

The recommended adult dose for VIRACEPT is 1250 mg twice daily (eg, 5 x 250 mg tablets BID) or 750 mg 3 times daily (3 x 250 mg tablets TID) in combination with nucleoside analogues. To reduce pill burden and increase compliance in HIV-infected patients, a higher strength tablet of 625 mg nelfinavir mesylate was developed.

Two bioequivalence studies (AG1343-712 and AG1343-713, fasted and fed, respectively) showed that nelfinavir mesylate 625 mg tablets is not bioequivalent to the commercial VIRACEPT 250 mg tablets. The area under the curve (AUC) increased 24% with the 625 mg tablet in Study AG1343-713, the fed study **(Table 1)**. However, the Cmax parameter was within the no effect range of 0.80 to 1.25. For the fasted study, Study AG1343-712, the AUC increased 32-34% and the Cmax increased 24% with the 625 mg tablet.

Due the modest increase in bioavailability, a retrospective review of safety data available from 6 VIRACEPT studies as listed below has been undertaken to determine whether potential new safety concerns could arise as a result of increased nelfinavir blood levels.

- AG1343-503: A Pilot, Phase II, Open-label, Dose-range–finding Study of AG1343 in HIV-positive Patients. Patients were randomized to 1 of 3 dosages: VIRACEPT 500, 600, or 750 mg twice daily. After the twice-daily dosing groups completed the 28-day core study, additional patients were randomized to 1 of 3 dosages: VIRACEPT 500, 750, or 1000 mg 3 times daily. Treatment duration was 28 days.
- AG1343-510: A Phase I/II Pilot study of VIRACEPT ™ (AG1343) in Combination With Stavudine (d4T) Versus Stavudine (d4T) Alone in HIV-positive Patients. This study was designed to evaluate the safety and efficacy of 3 dosages of VIRACEPT and patients were randomized to 1 of 4 treatment arms: VIRACEPT 500 mg 3 times daily plus stavudine, VIRACEPT 750 mg 3 times daily plus stavudine, VIRACEPT 1000 mg 3 times daily plus stavudine, or stavudine alone. Treatment duration was 56 days.
- AG1343-511: A Phase III Randomized, Double-blind, Placebo-controlled Study of VIRACEPT ™ in Combination With Zidovudine (AZT)+Lamivudine (3TC) Versus AZT+3TC Alone in HIV-positive Patients with <1 Month or No Prior Antiretroviral Treatment. The three treatment arms are 1) VIRACEPT 500 mg TID + AZT + 3TC; 2) VIRACEPT 750 mg TID + AZT + 3TC; and 3) Placebo TID + AZT + 3TC.
- AG1343-542: A Phase III Study Comparing BID and TID Dosing of VIRACEPT ™ in Combination with Stavudine (d4T)+Lamivudine (3TC) in HIV-positive Patients. The study was initially designed to evaluate 4 different dose levels (750 mg twice daily, 1000 mg twice daily, 1250 mg twice daily, and 750 mg 3 times daily) of VIRACEPT in combination with d4T and 3TC. However, after the data from Study 511 became available, the study was amended to only include two groups: 1250 mg BID and 750 mg TID.
- Study 0073A: an open-label randomized study of delavirdine mesylate (DLV; RESCRIPTOR®) plus nelfinavir (NFV), didanosine (ddI), and stavudine (d4T) in triple and quadruple treatment regimens in HIV-1-infected individuals. This study was a phase IIIb, open-label, parallel-group, randomized, multicenter study comparing quadruple therapies of delavirdine (400 or 600 mg 3 times daily), nelfinavir, didanosine, and stavudine. The two arms of the study were DLV (600 mg TID) + NFV (750 mg TID) + d4T (dosed by body weight) + ddI (dosed by body weight) and DLV (400 mg TID) + NFV (750 mg TID) + d4T (dosed by body weight) + ddI (dosed by body weight).

- Study 0073B: an open-label randomized study of delavirdine mesylate (DLV, RESCRIPTOR®) plus nelfinavir (NFV), didanosine (ddI), and stavudine (d4T) in triple and quadruple treatment regimens in HIV-1-infected individuals. Study 0073B was a phase IIIb, open-label, parallel-group, randomized, multicenter study comparing triple and quadruple combination therapies of delavirdine, nelfinavir, didanosine, and stavudine. Duration of participation in the study was 24 weeks with 3 optional 24-week extension periods. Patients were randomized to receive 1 of the 4 following treatment regimens:1) DLV (600 mg BID) + NFV (1250 mg BID) + d4T (30 or 40 mg BID according to weight); 2) DLV (600 mg BID) + NFV (1250 mg BID) + ddI (125 or 200 mg BID according to weight); 3) NFV (1250 mg BID) + d4T (30 or 40 mg BID according to weight) + ddI (125 or 200 mg BID according to weight); 4) DLV (600 mg BID) + NFV (1250 mg BID) + d4T (30 or 40 mg BID according to weight) + ddI (125 or 200 mg BID according to weight).

Only the individuals whose AUC were available from the first 4 studies were pooled for the analysis. There were total of 317 subjects in the pooled data set, including 63 subjects from study 503, 23 subjects from study 510, 174 subjects from study 511, and 57 subjects from study 542. The daily dose for the four studies are summarized in the following table:

Study	Daily dose for nelfinavir
503	1500, 2250, 3000
510	1500, 2250,3000
511	1500, 2250
542	2500 and 2250

Exposure measured as AUC_{24} were divided into three ranges: <41, 41-61, and >61 mg•h/L and the adverse events in each range are summarized **Table 2-4**. The analysis showed that patients exposed to high plasma levels of nelfinavir (>61 mg.h/L) had a somewhat different adverse event profile from those patients with typical or low plasma levels of nelfinavir (41 to 61 or <41 mg.h/L, respectively), although adverse events were not consistently associated with higher concentrations when individual study data were examined. Asthenia and increased GGT (as an adverse event) were sometimes considered treatment related and were also associated with increasing exposure to nelfinavir in the individual studies making up pooled population. However, the sponsor concluded that neither of these is considered to represent an unacceptable risk of higher exposure to nelfinavir. Of the adverse events typically associated with nelfinavir, only diarrhea showed a tendency to increase with exposure. Nelfinavir-associated diarrhea is generally a manageable reaction and rarely interrupts therapy.

The safety data from two phase 3 studies (study 73A and 73B) were used to further support that the moderate increase in the 625 mg tablet was not a clinical concern. In Study 73A and 73B, there were total of 130 subjects who received three or four HIV drugs including nelfinavir and delavirdine. It is believed that these 130 subjects would have higher exposure of nelfinavir because three pharmacokinetic studies (Study 70, 73A, and 711) showed that co-administration of delavirdine with nelfinavir increases nelfinavir levels by 2- to 3-fold when compared to nelfinavir alone. The geometric mean values of nelfinavir AUC_{24} in Study 70, 73A and 711 were 148, 124 and 180 mg.h/L, respectively. The safety assessment of the two studies showed that the adverse events of diarrhea, nausea, flatulence, rash, and asthenia associated with these even higher levels of nelfinavir were not exacerbated by increased exposure. In addition, no new adverse events appeared outside the safety profile expected for VIRACEPT.

Based on the above 6 studies, the sponsor concluded that the safety profile for the new formulation is acceptable even though incidence of diarrhea might be higher for the new formulation because the

diarrhea is a manageable adverse event. On the other hand, the safety data from two phase 3 trials showed that no new adverse events appeared outside the safety profile expected for VIRACEPT.

The sponsor's analysis suggested that as compared with the current formulation, use of new formulation would result in more incidences of diarrhea. However, the analysis could not quantitate the increase of the incidence of diarrhea of using the new formulation. To quantitate the difference in adverse event between current and new formulation, an exposure-response relationship was established using the pooled data from the four studies. Using the exposure response relationship and the exposures of two formulations, the impact of different exposure of the two formulations on the incidence of adverse event was assessed.

Examination on the data indicated that a trend between incidence of adverse event and the exposure exist only for two events, diarrhea and Grade 2 rash. The logistic regression analysis was conducted by this reviewer and showed that there is no statistically significant association between Grade 2 rash and nelfinavir exposure measured as daily exposure (AUC_{24}). For diarrhea, among the 314 subjects in the data set, 246 subjects experienced diarrhea regardless of causality and severity, 222 subjects experienced nelfinavir related diarrhea, 86 subjects experienced Grade 2 and above diarrhea, and 64 subjects experienced nelfinavir related Grade 2 and above diarrhea. The logistic regression analysis was applied to test the association between the diarrheas and the AUC_{24} and the results are presented in **Table 5**. The results showed that nelfinavir related Grade 2 and above diarrhea is most significantly associated with AUC_{24} with the p value of 0.00530 (**Figure 1**). Using this relationship, the probability of having nelfinavir related Grade 2 and above diarrhea was predicted for the individuals in Study 713 (fed bioequivalence study) after taking current 250 mg tablet and new 625 mg tablet. The daily exposures (AUC_{24}) for Study 713 calculated as $2*AUC_{0-}$ after a single dose is used for predicting the probability of having nelfinavir related Grade 2 and above diarrhea. The results presented in **Table 6** and **Figure 2** show that the mean probability of having diarrhea for 250 mg tablet and 625 mg tablet are 0.31 and 0.37, respectively. It indicates that using new formulation would result in higher incidence of diarrhea but the increased incidence of diarrhea is only 6% (CI: 4%-9%).

Cautions need to be taken to interpret the predicted absolute probability of having diarrhea for each formulation due to the reasons that 1) the exposure used in exposure response relationship was obtained after multiple doses in phase 2/3 studies but the exposure used in Study 713 was obtained from a single dose phase 1 study. The evidence shows that the exposure of nelfinavir after multiple doses was decreased due to the possible self induction; 2) the exposure response data are obtained from phase 2/3 studies. The predicted probability of diarrhea is based on the assumption of full compliance. However, the less compliance of the drug in phase 3 studies may result in less adverse event rate than predicted. Nevertheless, the analysis quantitates the difference in incidence of diarrhea that resulted from different exposures of two formulations.

CONCLUSION:

1. This analysis demonstrated that the exposure response relationship could be used to quantitatively compare the adverse event of interest between two formulations when the two formulations are not bioequivalent.
2. This analysis shows that a higher probability of having diarrhea is associated with the use of new formulation.
3. Using the new formulation, the incidence of having diarrhea would be increased by 6% as compared to the current marketed formulation.

COMMENTS:

1. The safety comparison between the two formulations was focused on only diarrhea. Since the incidence of having other adverse event was lower, no relationship could be found between the other adverse events and the exposure.
2. The relationship between rash and exposure was examined; there is no association between rash and exposure.
3. The sponsor used the data from two phase 3 trials in which nelfinavir was used with delavirdine and the other drugs to support the safety of new formulation because a higher nelfinavir exposure was expected in these two trials. It needs to be pointed out that the two trials can be used to support the safety of the new formulation when new formulation is used without a metabolic inhibitor. The exposure would be higher when new formulation is co-administered with delavirdine as compared with the exposures in these two trials. Therefore, no safety data support the use of the new formulation with delavirdine.
4. This analysis was focused on the comparison between marketed and the new formulation. A caution needs to be taken when interpreting the absolute probability of diarrhea for each formulation. The exposures used for predicting the probability of diarrhea for the new formulation was obtained after the single dose in phase 1 study but the exposures used in exposure response relationship was obtained after multiple doses in phase 3 studies.

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Table 1. Summary of Pharmacokinetic Data from Bioequivalence Studies AG1343-712 and AG1343-713

	Geometric LS Mean (95% CI) Fasted (Study AG1343-712)		Ratio (90% CI) Fasted	Geometric LS Mean (95% CI) Fed (Study AG1343- 713)		Ratio (90% CI) Fed
Parameter (Units)	Treatment A[a] (N=27)	Treatment B[b] (N=27)	Treatment B vs Treatment A	Treatment A[a] (N=28)	Treatment B[b] (N=28)	Treatment B vs Treatment A
$AUC_{(0-\infty)}$ mg.h/L	16.2 (14.0-18.7)	21.4 (18.5-24.8)	1.32 (1.11-1.57)	35.7 (33.6-37.8)	44.2 (41.7-46.9)	1.24 (1.16-1.33)
AUC_{last} mg.h/L	15.5 (13.3-18.0)	20.8 (17.9-24.2)	1.34 (1.12-1.60)	34.9 (33.0-37.0)	43.4 (41.0-46.0)	1.24 (1.16-1.33)
^{C}max mg/L	2.34 (2.09-2.61)	2.91 (2.60-3.25)	1.24 (1.09-1.42)	4.62 (4.41-4.84)	5.31 (5.06-5.56)	1.15 (1.09-1.21)

a 5 x 250 mg VIRACEPT Tablets.
b 2 x 625 mg nelfinavir mesylate Tablets.

Table 2. Treatment-emergent Diarrhea, Nausea, Flatulence, and Rash Split by AUC

		AUC mg.h/L		
Adverse Event	**<41**	**41-61**	**>61**	**Total**
COSTART Term	**N=142**	**N=123**	**N=52**	**N=317**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Diarrhea				
All grades/all causalities	106 (74.6)	98 (79.7)	43 (82.7)	247 (77.9)
Grade 2+ (treatment related)	21 (14.8)	29 (23.6)	16 (30.8)	66 (20.8)
Nausea				
All grades/all causalities	63 (44.4)	55 (44.7)	19 (36.5)	137 (43.2)
Grade 2+ (treatment	4 (2.8)	6 (4.9)	2 (3.8)	12 (3.8)
related)				
Flatulence				
All grades/all causalities	23 (16.2)	32 (26.0)	10 (19.2)	65 (20.5)
Grade 2+ (treatment related)	3 (2.1)	4 (3.3)	0	7 (2.2)
Rash				
All grades/all causalities	29 (20.4)	32 (26.0)	9 (17.3)	70 (22.1)
Grade 2+ (treatment related)	1 (0.7)	2 (1.6)	1 (1.9)	4 (1.3)

Table 3. Treatment-emergent Cardiac Adverse Events Split by AUC

		AUC mg.h/L		
Adverse Event COSTART	**<41**	**41-61**	**>61**	**Total**
Term	**N=142**	**N=123**	**N=52**	**N=317**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Tachycardia	2 (1.4)	7 (5.7)	1 (1.9)	10 (3.2)
Syncope	1 (0.7)	2 (1.6)	1 (1.9)	4 (1.3)
Arrhythmia	1 (0.7)	2 (1.6)	0	3 (0.9)
Bradycardia	1 (0.7)	0	0	1 (0.3)
Sinus bradycardia	0	1 (0.8)	0	1 (0.3)
Abnormal ECG	1 (0.7)	0	0	1 (0.3)
Atrial fibrillation	1 (0.7)	0	0	1 (0.3)
Extrasystoles	0	0	1 (1.9)	1 (0.3)
Supraventricular extrasystoles	0	0	1 (1.9)	1 (0.3)
Heart failure	1 (0.7)	0	0	1 (0.3)
Right heart failure	1 (0.7)	0	0	1 (0.3)

Table 4. Marked Shifts in Laboratory Values in >1% of the Population Split by AUC

Laboratory	**<41 mg.h/L**	**41-61 mg.h/L**	**>61 mg.h/L**	**Total**
parameter	**N=142**	**N=123**	**N=52**	**N=317**
	n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**
Serum lipase	0/7 (0)	2/4 (50)	1/2 (50)	3/13 (23.1)
Creatine kinase	2/83 (2.4)	7/81 (8.6)	2/33 (6.1)	11/197 (5.6)
Neutrophils	6/142 (4.2)	4/123 (3.3)	3/52 (5.8)	13/317 (4.1)
Lymphocytes	3/142 (2.1)	7/123 (5.7)	1/52 (1.9)	11/317 (3.5)
Triglycerides	3/88 (3.4)	2/88 (2.3)	2/34 (5.9)	7/210 (3.3)
Glutamyl transferase	3/106 (2.8)	0/104 (0)	3/50 (6.0)	6/260 (2.3)
AST (SGOT)	5/142 (3.5)	1/123 (0.8)	2/52 (3.8)	8/317 (2.5)
ALT (SGPT)	3/142 (2.1)	1/123 (0.8)	3/52 (5.8)	7/317 (2.2)
Cholesterol	1/35 (2.9)	0/17 (0)	0/1 (0)	1/53 (1.9)
LDH	2/142 (1.4)	1/123 (0.8)	2/51 (3.9)	5/316 (1.6)
Hemoglobin	1/142 (0.7)	1/123 (0.8)	2/52 (3.8)	4/317 (1.3)

Table 5. The logistic regression analysis on diarrhea and daily nelfinavir exposure (AUC_{24})

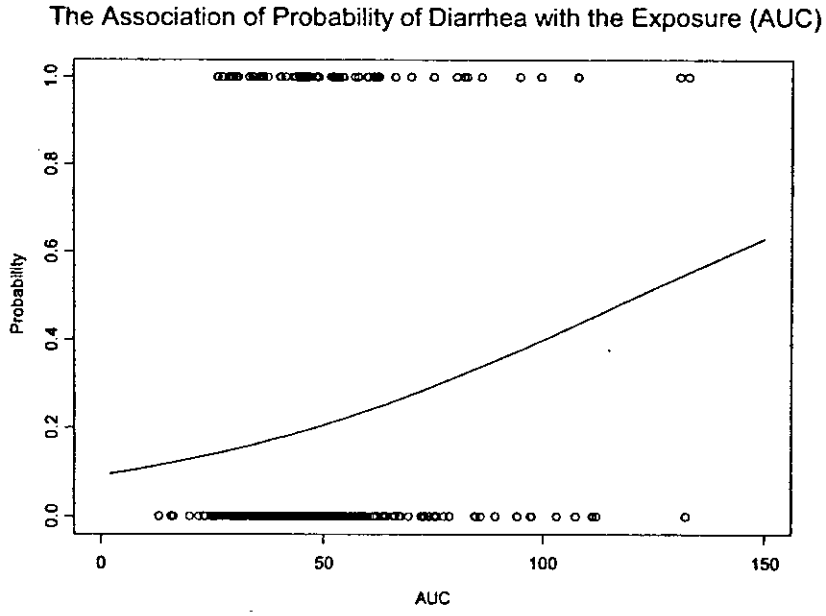
		Intercept (standard error)	Slope (standard error)	P value
All cause diarrhea	246	0.6021 (0.389)	0.0149 (0.00817))	0.057
Drug related diarrhea	222	0.2118 (0.3512)	0.0145(0.00727)	0.037
Grade 2^+ diarrhea	86	-1.74 (0.336)	0.0158 (0.00628)	0.0120
Grade 2^+ + drug related	64	-2.289 (0.366)	0.0188(0.00663)	0.00530

Table 6. The predicted probability of having diarrhea for Study 713

		250 mg tablet	625 mg tablet
AUC_{24} (mg/h•L)*	Mean	76.78	92.5
	Min-Max	22.26-130	43.6-173.2
Probability of having diarrhea	Mean	0.31	0.37
	Min-Max	0.13-0.54	0.17-0.72

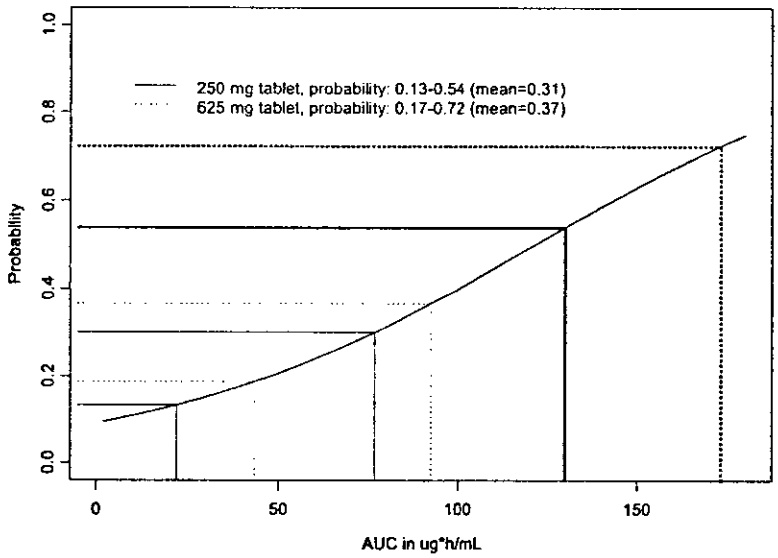
*: Based on the bid regimen, AUC_{24} was calculated as $2*AUC_{0-}$ which was obtained from a single dose study.

Figure 1



The circles represent the individual data; the line represents the predicted probability vs AUC_{24}

Figure 2



The solid lines represents the minimal, mean, and maximal probability of having diarrhea for 250 mg tablet; the dash lines represent the minimal, mean, and maximal probability of having diarrhea for 625 mg

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Robert Kumi
5/12/03 11:12:32 AM
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Kellie Reynolds
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BIOPHARMACEUTICS

Jenny Zheng
5/12/03 11:19:24 AM
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