CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-503

MEDICAL REVIEW(S)

NDA 21-503

VIRACEPT (NELFINAVIR MESYLATE) 625 MG FOR TREATMENT OF HIV INFECTION

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HFD - 530

CLINICAL REVIEW

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Clinical Review for NDA 21-503

Executive Summary

I. Recommendations

A. Recommendation on Approvability

It is recommended that the application of Viracept 625-mg formulation (nelfinavir mesylate), for the treatment of Human Immunodeficiency Virus (HIV) infection be approved. The 250 mg drug formulation has already been approved for the treatment of HIV infection for the past 6 years. The 625-mg formulation offers enhanced convenience of administration, a lower pill burden, which may potentially help with adherence, and a fair overall safety profile. This newer formulation is more bioavailable than the older formulation. The main risk is that of an increased probability of diarrhea with the 625-mg formulation.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1) Changes are needed in the labeling to reflect the following:

a) That the principal proarrhythmic risk of nelfinavir seems to originate from interference with the metabolic pathway of other proarrhythmic drugs. This is a potential risk.

Post-marketing data analysis revealed 5 cases of Torsades de Pointes and another 5 cases of increased QT interval, in patients on nelfinavir. Current labeling contains a bolded warning against use of nelfinavir, which is a CYP 3A4 inhibitor, with QT-prolonging drugs that are 3A4 substrates. The warning section of the label is being strengthened to address the use of NFV when co-administered with drugs that are metabolized by CYP3A4 and that prolong the QT interval. Additionally, QT prolongation and Torsades de Pointes adverse experiences have been added to the Post-Marketing Experience section of the label.

b) That NFV is metabolized by CYP2C19 and CYP3A4

2) Ongoing Pharmacovigilance, with periodic clinical reviews and cumulative reports on the 625mg-formulation.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Four VIRACEPT studies (AG 1343-503, AG1343- 510, AG1343-511 and AG 1343-542) for which data was previously submitted to FDA under NDA 20,779 were pooled and included in **Pooled Population 1 (PP1)** for safety analysis purposes. Subjects were selected on the basis of availability of pharmacokinetic(PK) data. Forty-eight weeks of safety data were reviewed. PP1 provided 317 patients for analysis.

Pooled population 2 (PP2) was formed by patients from Study 0073B (173 patients) and Study 0073A (23 patients). Study 0073B provided 130 patients receiving a combination of nelfinavir and delavirdine (an inhibitor of nelfinavir clearance), were exposed to considerably higher levels of nelfinavir, as compared to the 43 patients receiving nelfinavir without delaviridine.

The safety analysis was a retrospective one where adverse events were analysed in the 3 drug plasma level AUC ranges. An analysis was performed, comparing the number and severity of AE's in the low and typical drug range groups and the high drug level group. The high AUC group is expected to mirror the effects of higher exposure with the 625-mg formulation.

B. Efficacy

{See NDA 20-778 and 20-779}. No efficacy trials were conducted with the 625-mg formulation, since this formulation is more bioavailable than the 250-mg formulation, there is no reason to believe that it would be less efficacious. Efficacy of Viracept has been previously reviewed in NDA's 20-778 and 20-779.

C. Safety

The following are the conclusions of the safety analysis:

Examination of adverse events in PP1 population reveals few adverse events that are associated with an increase in NFV exposure.

1. Asthenia (representing mostly fatigue, tiredness, and weakness) was associated with increasing exposure to NFV in individual studies in PP1. The majority of the cases were related to the underlying condition of the patient or concurrent medication.

2. Increased GGT was associated with higher exposure to NFV. But the same association was not linked with any tendency toward co-elevation of ALT, AST, alkaline phosphatase and bilirubin, suggesting that there is no increased risk of hepatotoxicity with the Viracept 625-mg formulation.

3. Anemia was reported as a treatment-emergent AE, but not NFV- related adverse event.

4. Diarrhea showed a tendency to increase with exposure. NFV-associated diarrhea is generally a manageable reaction and infrequently interrupts therapy.

Adverse event conclusions in PP2

Comparison of PP2 (130 patients with safety data) to the group of 43 patients who did not receive DLV, complements the primary analysis of safety described in PP1.

There is a slight increase in diarrhea, nausea, flatulence, and asthenia, and there is an increased risk of these events at high concentrations of NFV. These results are not inconsistent with the trends seen in PP1, and suggest a small increased risk of these adverse events at high concentrations of NFV.

Also increase in skin rash were observed at rates of 31.5% for NFV+DLV vs 11.6% for NFV alone. There were no reports of a severe exfoliative skin reaction such as Stevens Johnson syndrome.

As in the PP1 studies, asthenia is increased slightly with increasing nelfinavir exposures in the PP2 patients.

Increased GGT as an adverse event was observed in the PP1 analysis, but was not seen when Pooled Population 2 was examined.

There was no evidence of a trend towards higher incidence of hematologic abnormalities in the PP2 group. There was also little tendency for abnormalities in ALT, AST, alkaline phosphatase, and bilirubin to increase with nelfinavir exposure, suggesting that there should be no increased risk of hepatotoxicity with the VIRACEPT 625-mg dosage regimen.

The conclusion is that the newer formulation has a greater probability of having diarrhea than the 250-mg formulation. Using statistical regression analysis and modeling, the increased incidence of diarrhea can be quantified to about a 6% increase in the probability of diarrhea. This increase may be clinically relevant. The relationship between skin rash and exposure was examined, and no association was demonstrated.

Most of the subjects in the trials were Caucasian and men. This demographic data suggests some lack of generalizability of findings, but in practice over the past 6 years, there were no race or gender-specific post-marketing safety issues.

All the protease inhibitors have the side effect of diarrhea. Diarrhea is most marked with NFV, and this AE is expected to be more severe with the 625-mg formulation.

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D. Dosing

The proposed treatment regimen is Viracept 1250 mg po bid, taken with food.

An exposure response relationship was established for Viracept 625 mg. A summary of the conclusions are noted in bulleted format below:

- Patients 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.

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

E. Special Populations

No gender differences were noted in pharmacology or safety issues.

Most of the study participants were male and Caucasian, and ethnic or racial issues were not specifically studied.

Clinical Review

I. Introduction and Background

Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name:	Nelfinavir mesylate
Trade name:	Viracept
Chemical:	[3*S*-[2(2*S**, 3*S**), 3α, 4aβ,8aβ]]-*N*-(1,1-dimethylethyl)decahydro-2-[2- hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide mono-methanesulfonate (salt)
Class:	Protease inhibitor
Proposed indication:	Treatment of HIV infection
Dosage and regimen:	625-mg po bid
Dosage form:	625-mg tablets

Viracept (nelfinavir mesylate) is a potent and specific inhibitor of HIV protease that received accelerated approval for the treatment of HIV infection in the USA in March 1997. Viracept received traditional approval in May 2000.

Viracept is active against the Human Immunodeficiency Virus (HIV) protease. The HIV protease cleaves polyproteins into functional protein products during the late stages of HIV replication. Nelfinavir binds to the active site of HIV protease and prevents cleavage of polyproteins, resulting in the formation of immature, non-infectious viral products.

Nelfinavir demonstrated additive to synergistic effects against HIV in double and triple combinations with reverse transcriptase inhibitors, zidovudine (AZT), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T), without enhanced toxicity.

An update of the original submission was provided in February 2000, and a Periodic Safety Update Report (PSUR) was submitted in May 2002. This report covered the period of April 2001 – March 2002.

Currently, the recommended adult dose of Viracept is 1250 mg twice daily or 750 mg three times daily, in combination with other antiretrovirals. Viracept currently is marketed as a 250-mg tablet. A more convenient 625-mg pill formulation was developed by the Sponsor, in an effort to reduce pill burden, and increase patient medication compliance.

Viracept 625 mg contains the same components as the commercial 250 mg tablet, with the addition of silicon dioxide, the removal of a dye, and with differences in ——— manufacturing process. Results of bioequivalence testing (Study 1343-712 and 1343-713) showed that patients receiving this new 625-mg formulation may be exposed to higher levels of nelfinavir and increased adverse events might be expected. There was an increase in AUC of 24% in the fed study (AG1343-713), however the C_{max} was in the bioequivalence range of 0.80-1.25. For the fasted study, (AG1343-712), there was an increase in AUC of 32-34% and an increase in C_{max} of 24%.

Due to the potential for higher exposure, consideration of the above pharmacokinetic results prompted a more thorough review of the safety of this new drug formulation in the form of a retrospective assessment of safety data from selected studies with measured PK data and higher AUC_{24} Viracept levels.

Analysis of the data sets of populations of PP1, and PP2 showed an upper and lower quartile for AUC_{24} of 41 and 61 mg.h/L. This submission examines treatment-emergent adverse events occurring with plasma levels <41, 41-61, >61 mg.h/L nelfinavir exposure groups in order to define the impact of increased nelfinavir exposure on safety parameters.

A. State of Armamentarium for Indication(s)

There are presently 3 classes of drugs approved for the treatment of HIV infection, in the following drug categories: -

1) Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

2) Nucleoside Reverse Transcriptase Inhibitors (NRTI)

3) Protease Inhibitors (PI)

Undoubtedly these drugs are effective against HIV, as evidenced by the improved mortality and morbidity of patients with HIV infection.

This new formulation offers a more convenient dosage form, which may enhance patient medication compliance, and may produce a more sustainable, long-term antiretroviral response.

A fourth category of anti-HIV drugs, namely **Fusion and Attachment Inhibitors** are presently undergoing clinical trial development, and the first drug to be approved in this category (Fuzeon or T20], was approved in March 2003.

B. Important Milestones in Product Development

- Approval of Viracept for treatment of HIV infection in March 1997, based on 24-week efficacy and safety study results (under NDA 20-779).
- Traditional approval of Viracept was based on 48 and 52 week efficacy and safety data in May 2000.
- Alternate Dosing Regimen of Viracept 1250 mg bid was approved on 1/26/99
- Update of original submission February 2000 (included safety data on 1862 patients)
- There were no major issues during clinical trials, in the areas of study design, safety, or ethics.

C. Other Relevant Information

Viracept (nelfinavir mesylate) Tablets, 250 mg and VIRACEPT (nelfinavir mesylate) Oral Powder, 50 mg/g are marketed in the United States by Agouron Pharmaceuticals, and were approved for marketing in the USA in March 1997, for the treatment of advanced HIV infection in selected patients, in combination with nucleoside analogues.

In January 1998, Viracept was granted marketing authorization in the 15 Member States of the European Union (EU). Marketing approval was received in Japan in March 1998. To date, Viracept is approved in over 80 countries worldwide, and is currently marketed in 38 countries.

Neither Japan Tobacco Inc. nor F.Hoffman-Roche Ltd. (who own the marketing rights in Europe) have informed Agouron Pharmaceuticals, Inc that the drug has been withdrawn from marketing for any reason related to safety or effectiveness.

This application looks retrospectively at safety parameters in pooled populations from the VIRACEPT NDA 20-779, comparing adverse events in low and typical plasma AUC groups, with those who had a higher steady-state exposure to nelfinavir.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The manufacturing process, quality control testing, and suppliers of the drug substance,

nelfinavir mesylate, remain unchanged from those described in NDA 20-779 for VIRACEPT 250 mg Tablets. Please refer to NDA 20-779 and all supplements for detailed Chemistry, Manufacturing and Controls information on Viracept.

The dosage form of Nelfinavir Mesylate 625 mg will be an immediate release tablet. The 625-mg tablets will be provided as white oval tablets, with clear film coating, debossed with "V" on one side and "625" on the other. Except for addition of — colloidal silicon dioxide as —, and the deletion of FD&C Blue #2 Powder dye, Nelfinavir Mesylate 625 mg Tablets contain the same components as commercial VIRACEPT 250 mg Tablets.

At the request of the Division of Antiviral Drug Products, Doctors Throckmorton and Stockbridge performed a Cardio-Renal Consultation on February 19th 2003. The consultation was requested because it was felt that post-marketing reports of Torsade de pointes, and QT prolongation, reported in a consultative review, performed by the Office of Drug Safety (ODS), represented a safety signal. Nearly all the cases of Torsades or QT prolongation on nelfinavir are confounded by the use of other drugs thought to prolong QT. The conclusions from this consultation were as follows:
"It is probably fair to conclude that a comprehensive evaluation of the arrhythmogenic potential of nelfinavir has not been done. However, it seems most likely that the principal proarrhythmic risk comes from interference with the metabolic pathways of other clearly proarrhythmic drugs. In this regard, the bolded warning could be improved by ———————————————————

The results of an Exposure-Response Consultation performed by Dr Jenny Zheng are relevant, and are discussed in greater detail in Section III B (Pharmacodynamics).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The absolute bioavailability of Viracept has not been determined. When the 625mg tablets were compared to the 250mg tablets at a single dose of 1250mg in healthy volunteers, under fed conditions, the AUC was 24% higher, while the C max was bioequivalent. In the fasted state, the AUC was increased by 33%.

In vitro, multiple cytochrome P-450 isoforms including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. However, CYP3A and CYP2C19 appear to be the predominant enzymes for nelfinavir metabolism in humans, and only CYP3A was inhibited at concentrations in the therapeutic range.
The *in vitro* metabolism data indicated that the enzymes responsible for nelfinavir metabolism had the following order of potency:

CYP3A4 > CYP2C19 > CYP2D6 > CYP2C9.

In vivo drug-drug interaction and metabolism data showed that delavirdine (CYP3A4 and CYP2C19 inhibitor) inhibited nelfinavir metabolism to a greater extent than ritonavir (CYP3A4 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.

The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750-mg dose containing ^{14}C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

Study AG1343-713 showed that the 625 mg dose had a C_{max} of 5.3(5.1-5.6), and AUC <infinity> 26.5 (25-28.1). The terminal half-life in plasma was typically 3.5 to 5 hours. Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750-mg dose of ^{14}C-nelfinavir.

The conclusions from the Clinical-Pharmacological review are noted in bulleted format below:

- 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 CYP3A4 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 CYP3A4.
- Based on a cross study-comparison (Study 713 vs. 712), food increases (2 to 3 fold) the AUC and C_{max} of nelfinavir of both the 250 mg and 625 mg tablets. The pharmacokinetic variability in the fasted state (> 50 %) is greater than in the fed state (< 40 %).

B. Pharmacodynamics

CYP2C19 poor metabolizers tend to have increased nelfinavir exposures. The pharmacokinetics of nelfinavir in CYP2C19 poor metabolizers are reviewed. Nelfinavir exposures of CYP2C19 poor metabolizers are approximately 2- to 3-fold of the median representative exposure of nelfinavir.

However, the exposures in CYP2C19 poor metabolizers are in the lower range of HIV patients who had the combination of VIRACEPT and RESCRIPTOR.

Exposure-Response Analysis assessed the impact of the difference in exposure between the two formulations (by Jenny J. Zheng PhD).

An exposure response relationship was established using pooled data submitted by the Sponsor. Diarrhea was the most common adverse event, and was associated with the increased exposure. The exposure-response relationship (explored via modeling and logistic regression analyses), were used to assess the impact of the increased bioavailability. In study 713, we looked at the predicted probability of diarrhea for the 250-mg and the 625-mg tablet. The results showed that there was a 6% higher probability of having diarrhea associated with the 625-mg new formulation. The mean probability of having diarrhea is 37% and 31% for new 625-mg vs the current 250-mg marketed formulation, respectively. The difference in the risk incidence of diarrhea was 6%, with a greater risk of diarrhea in the 625-mg group.

The conclusion is that the newer formulation has a greater probability of having diarrhea than the 250-mg formulation. This increased incidence of diarrhea can be quantitated to about a 6% increase in the probability of diarrhea. This increase may be clinically relevant, and a description will be included in the product labeling.

IV. Description of Clinical Data and Sources

A. Overall Data

The data that was analyzed for determination of the safety of the Viracept 625-mg formulation, included data from numerous primary and secondary sources:

Primary sources:

- The applicant's Integrated Summary/ Analysis of Safety -NDA 21,503 (Viracept), conducted using volumes 1 to 19, and electronic SAS transport (JMP) files of the electronic submission.
- Adverse event tables in the NDA submission
- Case report forms for patients for patients who experienced serious adverse events

- Applicant's narrative summaries of deaths, serious adverse events and other events that resulted in dropout.

Secondary sources:

The secondary sources served as a critical source of information for review, as they provided a larger database needed to look at low-rate serious events, and included the following:

- Post Marketing Data – including the, Periodic Safety Update Report (PSUR) for Viracept (nelfinavir mesylate) NDA # 20-779, and Oral Powder # 20-778, covering the period April 01 2001 to March 31,2002, containing 7 volumes of data.

- Results of *in vitro* animal investigations, designed to evaluate the effects of Nelfinavir and its metabolites on the HERG Potassium channels and the effects of Different Stimulation rates on action potentials recorded from isolated Dog Purkinje fibres in vitro in the presence of AG 1346. (Report No. AG 001346/IC/002/02 submitted to IND 48,124 on June 24, 2002).

- Analysis of the safety of Viracept for cardiac adverse effects in Pooled Population 1.

- Updated review for Torsades de Pointes and QT prolongation Reports in association with the use of Viracept provided by the Sponsor.

B. Tables Listing the Clinical Trials

Pooled Population 1

Protocol # Title Countries	Design	Treatment Dose, Frequency Duration	# "Safety Evaluable" patients with PK data Total # patients with PK data in pooled population
Study AG1343-503 2 sites - USA	Pilot, phase II, Open-label, dose-range-finding study in HIV + patients	500, 600 , 750 mg bid then 500, 750, 1000 mg tid Duration 28 days; extension 24 months	63 317
Study AG1343-510 3 sites - USA	Phase I/II pilot study of viracept in combination with Stavudine(d4T) vs D4T alone in HIV + patients	500 mg tid +d4T 750 mg tid +d4T 1000 mg tid+d4T d4T Duration 56 days; extension 12 months of commercially available	23 317
Study AG1343-511	Phase III Randomized, double-blind, placebo controlled study of Viracept in combination with zidovudine(AZT) + Lamivudine(3TC) vs AZT+3TC alone in treatment naïve HIV + patients	500 tid+AZT+3TC 750 tid+AZT+3TC Placebo tid+AZT+3TC Duration 24 week core; extension 6 months + long term extension	174 317
Study AG1343-542	Phase III randomized, open label study comparing bid and tid Viracept in combination with d4T+3TC in HIV + patients,	1250 mg bid+d4T+3TC 750 mg tid+d4T+3TC Duration 48 weeks	57 317

Pooled Population 2

Protocol # Title Countries	Design	Treatment Dose, Frequency Duration	# "Safety Evaluable" patients with PK data Total # patients with PK data in pooled population
M/3331/0073A	Phase IIIb,open-label, randomized study of delaviridine mesylate(DVL)+nelfinavir (NFV)+didanosine(ddI)+d4T in HIV-1 infected individuals	2 treatment groups: - DLV 600 mg tid+NFV 750 mg tid+d4T+ddI - DLV 400 mg tid+NFV 750 mg tid+d4T+ddI Duration up to 96 weeks in extension	22 195
M/3331/0073B	Phase IIIb, open-label, parallel group, randomized study of DLV+NFV+ddI+d4T in HIV-1 infected individuals	4 treatment regimens: - DLV 600 mg bid+NFV 1250 mg bid+d4T - DLV 600 mg bid+NFV 1250 mg bid+ddI - NFV 1250 mg bid+d4T bid+ddI bid - DLV 600 mg bid+NFV 1250 mg bid+d4T bid+ ddI bid	173* 195

Source: FDA compilation of summary tables of pooled populations 1 and 2

* PK imputed from dose

V. Clinical Review Methods

NDA 21-503 examines the treatment emergent adverse events in the AUC-24 plasma level groups and defines the impact of increased exposure on safety parameters.

A. How the Review was conducted

The safety review was accomplished by reviewing the adverse events, laboratory abnormalities, and discontinuations of therapy due to adverse events from Pooled-Populations 1 and 2, consisting of 317 patients and 130 patients respectively, evaluable for safety.

In the case of PP1, the safety analysis presents treatment–emergent adverse events split by AUC categories, indicating low, typical, and high exposures to NFV. In the case of PP2, the safety analysis presents treatment emergent adverse events comparing all patients receiving DLV and NFV (predicting higher NFV levels), and to those receiving NFV without DLV.

The following subsections are addressed for each pooled population, namely:

- All causality treatment –emergent adverse events of at least grade 1 severity, where there is a trend for increased reporting with increased exposure to NFV.
- The relationship to exposure of the drug related adverse events most commonly associated with NFV
- Discontinuation due to adverse events
- Laboratory abnormalities
- Possible arrhythmogenic activity

B. Overview of Materials Consulted in Review

- Primary source data

  1. NDA 21-503
  2. PSUR (4/2001- 3/2002)

- Secondary source data

- Post marketing adverse event reporting (Spontaneous Reporting)
- AE Safety reports in other markets (Europe, Japan)
- The literature
- Patient databases and registries

C. Overview of Methods Used to Evaluate Data Quality and Integrity

New Efficacy studies were not performed as part of this submission.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All clinical trials were conducted in accordance with acceptable ethical standards.

E. Evaluation of Financial Disclosure

Financial disclosures submitted by the Sponsors were examined by the Agency. There are no issues related to this disclosure.

F. Individual Study Reports

Study AG1343-503

Title: A pilot, phase II. Open-label, dose-range finding of Viracept in HIV-positive patients.

Design: Study 503 was a Phase II, open label, dose-range finding study on HIV positive patients conducted at 2 sites in the USA. Patients were randomized to one of three dosages, 500 mg, 600 mg or 750 mg bid. After patients completed the 28 day twice daily core study, further patients were randomized to 500 mg, 750 mg or1000 mg three times daily for 28 days.

Study population:

The study population consisted of 97% males and 3% females, of which 94% were Caucasian and 6 % were Black. The mean age of the population was 38.8 years (range 24-58 years). The mean baseline CD4 count was 335, with a standard deviation of 133. The mean $\log_{10}$HIV RNA was 4.84, with a standard deviation of 0.33. There is no significant difference in baseline demographic data between study 503 and the other components of pooled population 1.

Extension Phase: During the extension phase of the study, patients were eligible to continue Viracept for 24 months at their prior tid dosage level, and with the addition of 2 NRTI's as allowed after consultation with the sponsor's medical monitor.

This study provided 63 "safety evaluable" patients with steady state PK data for analysis in the PP1 population.

Study AG1343-510

Title: Phase I/II, pilot, open-label, randomized, study of Viracept in combination with Stavudine(d4T) vs d4T alone in HIV-positive patients.

Design: Study 510 was a Phase I/II, open label, randomized study of Viracept in combination with d4T vs d4T alone in HIV positive patients, designed to evaluate safety and efficacy. Study was conducted at 3 sites in the USA. Patients were randomized to one of 4 treatment arms:

Viracept 500 mg tid + d4T
Viracept 750 mg tid + d4T
Viracept 1000 mg tid+ d4T
D4T alone

The study duration was 56 days.

Study population: The study population was 91% males, 83% white, with a mean age of 37 years (+/- 6 years). Mean baseline CD4 count was 342 and mean $\log_{10}$ HIV RNA was 4.7. There was no significant difference in baseline demographics between this study population and the remainder of patients in Pooled Population 1.

The extension phase lasted for 12 months or until the product became commercially available.
This study provided 33 "safety evaluable" patients with steady state PK data for the PP1.

AG1343-511

Title: Phase III, randomized, double-blind, placebo controlled study of Viracept in combination with AZT and lamivudine (3TC) versus AZT+3TC alone in HIV-positive patients with < 1 month or no prior antiretroviral treatment.

Design: Study 511 was a double-blind, placebo-controlled, randomized Phase III study designed to compare the efficacy and safety of Viracept (750 or 500 mg tid) in combination with AZT and 3TC versus placebo in combination with AZT and 3TC. The study had 3 phases: a 24-week core study, a 5-month extension phase and a long-term extension phase.

Patients were required to be essentially antiretroviral naïve with a plasma HIV RNA level of
> 15,000 copies/ml and were randomized to 1 of 3 treatment groups:

Viracept 500 mg bid +AZT+3TC
Viracept 750 mg tid + AZT + 3TC
Placebo tid + AZT + 3TC

The CD4 lymphocyte count was used in the randomization to balance treatment groups.

Patients who experienced treatment failure while receiving Viracept or placebo, were allowed to have their regimen altered to include new reverse transcriptase inhibitors and continued taking Viracept; however, use of other protease inhibitors was prohibited.

Study population

The study population was 89% male, and 78% white, with a mean age of 36.8 years. The mean CD4 count was 294, and the $\log_{10}$ HIV RNA was4.87. There were no significant differences in baseline demographic data between this group of patients and the other components of PP1.

This study provided 174 "safety evaluable" patients with steady state PK data to Pooled-Population 1.
The core phase of the study lasted 24 weeks, a 6-month extension phase, and a long-term extension phase.

<u>AG1343-542</u>

Title: Phase III study comparing bid and tid dosing of Viracept in combination with stavudine(d4T) + lamivudine (3TC) in HIV positive patients.

Design: This study was initially designed to evaluate 4 dose levels of Viracept. However, when the results of study 511 became available, demonstrating that the 750 mg 3-times–daily dose was superior to a 500 mg 3 times a day dose, in terms of HIV RNA suppression, the study was amended. It was modified to become a randomized, open-label, 2 group comparative study of 2 Viracept dose regimens, each in combination with d4T and 3TC. The 2 groups consisted of: Viracept 1250 mg bid + 3TC + d4T group and Viracept 750 mg tid + 3TC + d4T.

Study population:

The study population was 93% male, and 95% white, with a mean age of 37.6 years. The mean CD4 count was 259, and the $\log_{10}$ HIV RNA was 5.10. There were no significant

differences in baseline demographic data between this group of patients and the other components of PP1.

Extension Phase

This study provided 54 "safety evaluable" patients with steady state PK data to PP1 The study duration was 48 weeks.

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Table showing Demographics of Pooled Population 1

Table 4. Pooled Population 1 Demographic Characteristics

	Number (%) of Patients			
Baseline Characteristics	**<41 mg.h/L (N=142)**	**41-61 mg.h/L (N=123)**	**>61 mg.h/L (N=52)**	**Total (N=317)**
Age (Yrs)				
Mean	36.6	37.8	38.3	37.3
Std. Dev.	8.4	9.0	8.0	8.6
Minimum	23.0	21.0	25.0	21.0
Maximum	60.0	66.0	58.0	66.0
Gender				
Female	13 (9.2)	8 (6.5)	6 (11.5)	27 (8.5)
Male	129 (90.8)	115 (93.5)	46 (88.5)	290 (91.5)
Race				
Caucasian	122 (85.9)	101 (82.1)	45 (86.5)	268 (84.5)
Black	10 (7.0)	11 (8.9)	5 (9.6)	26 (8.2)
Asian	2 (1.4)	2 (1.6)	1 (1.9)	5 (1.6)
Other	8 (5.6)	9 (7.3)	1 (1.9)	18 (5.7)
$^{Log}_{10}$ RNA PCR (Std. Assay)				
Mean	4.9	4.9	4.7	4.9
Std. Dev.	0.5	0.4	0.4	0.4
Minimum	3.4	4.1	4.0	3.4
Maximum	6.1	6.0	5.7	6.1
CD4 Count (cells/$mm^{3)}$				
Mean	301	304	283	300
Std. Dev.	189	191	170	187
Minimum	10	10	10	10
Maximum	1066	1008	584	1066
CD8 Count (cells/mm^3)				
Mean	984	1117	1004	1039
Std. Dev.	618	569	449	576
Minimum	195	155	187	155
Maximum	5255	2899	2005	5255

Table 8. **Pooled Population 1: Frequency of All-causality Treatment-emergent Adverse Events Exhibiting Exposure Dependence Split by AUC**

	AUC mg.h/L			
Adverse Event COSTART Term*	**<41 N=142**	**41-61 N=123**	**>61 N=52**	**Total N=317**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Asthenia	39 (27.5)	38 (30.9)	20 (38.5)	97 (30.6)
Lymphadenopathy	13 (9.2)	16 (13.0)	8 (15.4)	37 (11.7)
Pharyngitis	13 (9.2)	16 (13.0)	7 (13.5)	36 (11.4)
Rectal discharge	10 (7.0)	12 (9.8)	6 (11.5)	28 (8.8)
Dermal fung	7 (4.9)	8 (6.5)	4 (7.7)	19 (6.0)
Eye disorder	6 (4.2)	8 (6.5)	4 (7.7)	18 (5.7)
Chest pain	7 (4.9)	7 (5.7)	3 (5.8)	17 (5.4)
Infection viral	3 (2.1)	9 (7.3)	4 (7.7)	16 (5.0)
Acne	4 (2.8)	7 (5.7)	4 (7.7)	15 (4.7)
Ecchymosis	4 (2.8)	6 (4.9)	4 (7.7)	14 (4.4)
Flu syndrome	4 (2.8)	5 (4.1)	4 (7.7)	13 (4.1)
Hypertension	4 (2.8)	5 (4.1)	3 (5.8)	12 (3.8)
Weight decreased	4 (2.8)	5 (4.1)	3 (5.8)	12 (3.8)
Chills	2 (1.4)	4 (3.3)	4 (7.7)	10 (3.2)
Hematuria	3 (2.1)	4 (3.3)	3 (5.8)	10 (3.2)
Increased GGTP	3 (2.1)	3 (2.4)	3 (5.8)	9 (2.8)
Herpes simplex	3 (2.1)	3 (2.4)	2 (3.8)	8 (2.5)
Edema	2 (1.4)	3 (2.4)	2 (3.8)	7 (2.2)

Table 6. Pooled Population 1: Treatment-emergent Diarrhea, Nausea,

Flatulence, and Rash Split by AUC

Adverse Event COSTART Term	AUC mg.h/L <41 N=142 n (%)	41-61 N=123 n (%)	>61 N=52 n (%)	Total N=317 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 related)	4 (2.8)	6 (4.9)	2 (3.8)	12 (3.8)
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)

Pooled Population 2

PP2 consisted of patients enrolled in 2 studies 0073A and 073B listed below.

M/3331/0073A
Title: An open label randomized study of delavirdine mesylate (DLV) plus nelfinavir (NFV), didanosine (ddI) and stavudine (d4T) in triple and quadruple treatment regimens in HIV-1-infected individuals.

Design: Study 0073A was a phase IIIB, open-label, parallel-group, randomized, multicenter study comparing quadruple therapies of DLV 400 mg or 600 mg 3 times daily, NFV 750 mg tid, ddI and d4T (according to body weight).
The main inclusion criteria were that patients be HIV infected; 14 years or older; have a CD4 cell count of at least 50 cells/mm3; have a plasma HIV RNA level of > 20,000 copies/mL; have no previous experience with NNRTI's, protease inhibitors or stavudine; and have less than 1 month exposure to didanosine.

Study population

Our analysis of the study population showed that 82% were male, 91% white, with an average age of 37.5 years. The mean baseline CD4 count was 408, and the $\log_{10}$ HIV RNA was 4.8.

This study provided 22 "safety evaluable" patients with steady state PK data for Pooled-Population 2. The study duration was for a 24-week period, with the option of continuing participation for 2 additional 24-week periods at the investigator's discretion.

Evaluation of Safety

Safety variables were performed on all patients, with the required samples collected at week 4.

The primary pharmacokinetic variables for both DLV and NFV were C max, AUC t and C min.

Table 23. Study 0073A: Frequency of All-causality Treatment-emergent Adverse Events in >10% of the Patients

Adverse event	DLV (600 mg) +	DLV (400 mg) +	Total
COSTART Term	NFV + d4T + ddI	NFV + d4T + ddI	N=22
	N=11	N=11	n (%)
	n (%)	n (%)	
Diarrhea	9 (81.8)	7 (63.6)	16 (72.7)
Nausea	5 (45.5)	5 (45.5)	10 (45.5)
Rash	4 (36.4)	4 (36.4)	8 (36.4)
Infection	4 (36.4)	4 (36.4)	8 (36.4)
Sinusitis	4 (36.4)	3 (27.3)	7 (31.8)
Abdominal pain	3 (27.3)	2 (18.2)	5 (22.7)
Accidental injury	4 (36.4)	1 (9.1)	5 (22.7)
Asthenia	4 (36.4)	1 (9.1)	5 (22.7)
Headache	1 (9.1)	3 (27.3)	4 (18.2)
Vomiting	1 (9.1)	3 (27.3)	4 (18.2)
Skin disorder	1 (9.1)	3 (27.3)	4 (18.2)
Gastroenteritis	1 (9.1)	2 (18.2)	3 (13.6)
Tooth disorder	1 (9.1)	2 (18.2)	3 (13.6)
Insomnia	2 (18.2)	1 (9.1)	3 (13.6)
Pharyngitis	1 (9.1)	2 (18.2)	3 (13.6)
Anxiety	2 (18.2)	1 (9.1)	3 (13.6)

Source: Appendix 8 Table 3.

M/3331/0073B

Title: An open label randomized study of delavirdine mesylate (DLV) Plus nelfinavir (NFV), didanosine (ddI) and stavudine (d4T) in triple and quadruple treatment regimens in HIV-1-infected individuals.

Design: Study 0073B was a phase IIIB, open-label, parallel-group, randomized, multicenter study comparing triple and quadruple therapies of DLV 400 mg or 600 mg 3 times daily, NFV 750 mg tid, ddI and d4T (according to body weight).
The main inclusion criteria were that patients be HIV infected; 14 years or older; have a CD4 cell count of at least 50 cells/mm3; have a plasma HIV RNA level of > 20,000 copies/mL; have no previous experience with NNRTI's, protease inhibitors or stavudine; and have less than 1 month exposure to didanosine.

Study population:
The study population was 81% male, 61 % white, with a mean age of 37.2 years. The mean baseline CD4 count was 4.82 and the $\log_{10}$ HIV RNA was 4.9. This study provided 173 "safety evaluable" patients with steady state PK data to PP2.

The study duration was for 24-week period, with 3 optional 24-week extension periods. No PK data was collected, and all PK data was imputed from the nelfinavir PK data in the 0073A study.

Table 24. Study 0073B: Frequency of All-causality Treatment-emergent Adverse Events in >5% of the Patients

Adverse Event COSTART Term	DLV + NFV + d4T	DLV + NFV + ddI	NFV + d4T + ddI	DLV + NFV + d4T + ddI	Total N=173
	N=43	N=45	N=43	N=42	n (%)
	n (%)	n (%)	n (%)	n (%)	
Diarrhea	24 (55.8)	29 (64.4)	24 (55.8)	22 (52.4)	99 (57.2)
Nausea	10 (23.3)	14 (31.1)	9 (20.9)	13 (31.0)	46 (26.6)
Rash	18 (41.9)	9 (20.0)	5 (11.6)	14 (33.3)	46 (26.6)
Vomiting	5 (11.6)	10 (22.2)	5 (11.6)	8 (19.0)	28 (16.2)
Headache	13 (30.2)	7 (15.6)	4 (9.3)	2 (4.8)	26 (15.0)
Infection	10 (23.3)	8 (17.8)	6 (14.0)	6 (14.3)	30 (17.3)
Asthenia	6 (14.0)	6 (13.3)	4 (9.3)	5 (11.9)	21 (12.1)
Neuropathy	7 (16.3)	7 (15.6)	1 (2.3)	0	15 (8.7)
Pharyngitis	4 (9.3)	5 (11.1)	3 (7.0)	3 (7.1)	15 (8.7)
Sinusitis	2 (4.7)	6 (13.3)	6 (14.0)	1 (2.4)	15 (8.7)
Back pain	3 (7.0)	6 (13.3)	3 (7.0)	2 (4.8)	14 (8.1)
Herpes simplex	4 (9.3)	5 (11.1)	4 (9.3)	1 (2.4)	14 (8.1)
Abdominal pain	4 (9.3)	4 (8.9)	2 (4.7)	3 (7.1)	13 (7.5)
Cough increased	1 (2.3)	6 (13.3)	4 (9.3)	2 (4.8)	13 (7.5)
Dry skin	5 (11.6)	2 (4.4)	1 (2.3)	2 (4.8)	10 (5.8)
Fever	2 (4.7)	2 (4.4)	4 (9.3)	2 (4.8)	10 (5.8)
Maculopapular rash	4 (9.3)	2 (4.4)	2 (4.7)	2 (4.8)	10 (5.8)
Accident injury	0 (0)	3 (6.7)	2 (4.7)	4 (9.5)	9 (5.2)
Flu syndrome	2 (4.7)	1 (2.2)	5 (11.6)	1 (2.4)	9 (5.2)
Gastroenteritis	2 (4.7)	1 (2.2)	3 (7.0)	3 (7.1)	9 (5.2)
Depression	1 (2.3)	5 (11.1)	0 (0)	3 (7.1)	9 (5.2)
Dizziness	1 (2.3)	4 (8.9)	1 (2.3)	3 (7.1)	9 (5.2)
Bronchitis	2 (4.7)	4 (8.9)	2 (4.7)	1 (2.4)	9 (5.2)
Skin disorder	3 (7.0)	2 (4.4)	4 (9.3)	0 (0)	9 (5.2)

Source: NDA 21,503: Volume 15, table 24

V. Integrated Review Of Efficacy

Issues concerning efficacy of Viracept were already addressed in NDA # 20,779. This process culminated in the approval of Viracept for treatment of HIV infection, in March 1997 at a dosage of 750-mg three times daily.

[Please see NDA # 20,779]

VI. Integrated Review of Safety

A. Brief Statement of Conclusions

Adverse event conclusions in PP1

Examination of adverse events in PP1 population reveals few adverse events that are associated with an increase in NFV exposure.

Asthenia (representing mostly fatigue, tiredness, and weakness) was associated with increasing exposure to NFV in individual studies in PP1. The majority of the cases were related to underlying condition of the patient or concurrent medication.

Increased GGT was associated with higher exposure to NFV. But the same association was not associated with any tendency toward co-elevation of ALT, AST, alkaline phosphatase and bilirubin, suggesting that there was no increased risk of hepatotoxicity with the Viracept 625-mg formulation.

Anemia was reported as a treatment-emergent AE, but not a NFV- related adverse event. Prior placebo controlled studies of NFV indicated that anemia is a nucleoside analogue related AE.

Diarrhea showed a tendency to increase with exposure. NFV-associated diarrhea is generally a manageable reaction and infrequently interrupts therapy.

Adverse events conclusions in PP2

Comparison of PP2 (130 patients with safety data) to the group of 43 patients who did not receive DLV, functions to complement the primary analysis of safety described in PP1.

There is a slight increase in diarrhea, nausea, flatulence, and asthenia, and there is an increased risk of these events at high concentrations of NFV. These results are not inconsistent with the trends seen in PP1, and suggest

a small increased risk of these adverse events at high concentration of NFV.

Also an increase in skin rash was observed NFV+DLV 31.5% vs 11.6% NFV alone. There were no reports of a severe exfoliative skin reaction such as Stevens Johnson syndrome. Based on the known adverse event profile of DLV, it is likely that the increase in rash is attributable to DLV administration. As in the PP1 studies, asthenia is increased slightly with increasing nelfinavir in the PP2 patients.

Increased GGT as an adverse event was observed in 2 of 317 patients in the analysis of PP1, but was not seen when PP2 was examined. There was no evidence of a trend towards higher incidence of hematology abnormalities in the PP2 group. There was also little tendency for ALT, AST, alkaline phosphatase, and bilirubin to increase with nelfinavir exposure, suggesting that there should be no increased risk of hepatotoxicity with the VIRACEPT 625-mg dosage regimen. Overall, the adverse event data for PP1 do not suggest that there is a greater risk of nonspecific toxicity associated with higher exposure to NFV.

B. Description of Patient Exposure

Four VIRACEPT studies (AG 1343-503, AG1343- 510, AG1343-511 and AG 1343-542 for which data was previously submitted to FDA under NDA 20,779 were pooled and included in **Pooled Population 1 (PP1)** for safety analysis purposes. Subjects were selected on the basis of availability of pharmacokinetic data. Forty-eight weeks of safety data were reviewed.

Pooled population 2 (PP2) was formed by patients from Study 0073B (173 patients) and Study 0073A (23 patients). Study 0073B provided 130 patients receiving a combination of nelfinavir and delavirdine (a inhibitor of nelfinavir clearance, were exposed to considerably higher levels of nelfinavir, as compared to the 43 patients receiving nelfinavir without delaviridine.

Cumulative exposure over time

The Sponsor asserts that since marketing introduction of Viracept in March 1997, and up to the end of March 2002 approximately — patients have been exposed to Viracept oral tablet and — patients to Viracept oral powder. These crude estimates of patient exposure were based on data received — covering the period from January 1999 to December 2001. The sponsor estimates that patients receiving first-line therapy for HIV stay on treatment for 12-14

months, while those receiving second–line therapy for HIV typically stay on treatment for 9-11 months.

Based on the above assumptions, it is estimated that a total of — patients have been exposed to Viracept tablets and — patients have been exposed to the oral powder.

C. Methods and Specific Findings of Safety Review

The following materials were assembled and reviewed prior to writing this analysis :

- The sponsor's Integrated Summary/ Analysis of Safety
- Adverse event tables in the NDA submission
- Case Report Forms for patients who experienced serious adverse events (SAE), or patients who dropped out of study because of an adverse event
- Sponsor's narrative summaries of deaths, SAE's, and other events that resulted in drop-outs
- Common Technical Document (CTD) safety related sections, describing sponsor's approach to the safety evaluation and the sponsor's conclusions.
- Review of Periodic Safety Update Report 1 April 2001-31 March 2002 for Viracept (NDA # 20-779)

Findings of Safety Review:

1. Deaths

2. Other Serious Adverse Events

3. Dropouts and other significant Adverse Events

   A) Overall profile of drop outs
   B) Adverse events associated with dropouts
   C) Other significant adverse events

Deaths in patients of PP1 and PP2

Two deaths occurred in Pooled Population 1; both in study 511.
One patient in the 41 to 61 mg.h/L group died due to progressive multifocal leukoencephalopathy, and 1 patient in the >61 mg.h/L group died due to *Mycobacterium avium* complex. Neither of the deaths was considered by the Agency to be related to Viracept.

No deaths were noted in study 72A (PP2).

Two deaths were noted in study 73B (PP2). The first death was caused by Atherosclerotic Cardiovascular Disease, and the second by Castleman's disease (giant follicular lymph node hyperplasia). These deaths occurred in patients whose NFV was not boosted by Delaviridine.

Drop outs due to adverse events in pooled population 1

10 of 142 patients or 7.0 % patients in the low plasma level group discontinued due to adverse events, while 5 of 142 or 4.1% patients in the typical plasma level group discontinued due to adverse events; 3of 52 or 5.8% of patients in the high plasma level group discontinued due to adverse events.

There is no significant difference between the groups. There is no relationship between discontinuations due to adverse events, and exposure to NFV.

Total discontinuations due to specific events such as diarrhea, nausea, flatulence and rash in PP1, were less than 1%.

There were four discontinuations due to adverse events in Study 73A: One for a flu syndrome, another for elevated serum amylase and lipase, another for depression, and a fourth for emotional lability.

Limitation of safety analysis

In any safety analysis, one encounters many challenges and concerns in attributing AE to any one drug. Different factors contribute to this challenge:

1. Issues of poolability, where comparison of different designs and populations are combined. The consistency of findings across individual studies, and across pooled studies are most important in detecting a safety "signal."
2. Coding issues- where the subjectivity of Investigators and Monitors, issues of lumping and splitting of diagnoses, and incorrect diagnoses and coding.
3. Polypharmacy is part of the standard of care in HIV disease. All patients are on 3 or even 4 different anti-HIV medications. When an AE is noted, it may be impossible to definitively attribute the AE to any one drug.
4. Ethical issues also abound. When a patient has an AE, it may be unethical to subject that patient to rechallenge exercises.

D. Adequacy of Safety Testing

Adequacy of Patient Exposure and Safety Assessments

NFV was first approved in March 1997. Since then, it has been estimated that there have been a total of nearly — *patients exposed* to the oral tablet or oral powder, for a mean duration of time of approximately *12 months*..

The patient exposure was adequate because of the multiple clinical trial studies that have been conducted with Viracept, and based on the results of past marketing surveillance analysis, and an estimated exposure in nearly one million persons.

The safety of 625-mg Viracept was evaluated by reviewing the available safety data from multiple sources:

The ***NDA*** provided the best estimate of rates and changes in risk over time by comparing the adverse event rates in the typical and low plasma level groups with the higher-level exposure groups. The higher plasma level exposed patients were used as a surrogate for the higher exposures involved with the 625-mg Viracept formulation.

The ***PSUR*** was useful in looking at AE's with a wide spectrum of seriousness.

Post-marketing AE reporting, although likely to have been significantly under reported provided information on serious rare AE's that may not be reported until larger populations are exposed.

The Agency's ***Adverse Event Reporting System*** or ***Med Watch*** reports were also checked while compiling this review on safety.

All of the above sources were utilized in evaluating the safety of NFV 625-mg.

Diarrhea was the most common AE, and the only AE that seems to be related to increased exposure.

Asthenia, nausea, flatulence was thought to be related to underlying condition of the patient or concurrent medication.

All reasonably applicable tests were done to assess the safety of the drug.

Comparison of the frequency of adverse effects between the various dosing and plasma level groups, did not reveal any significant difference in the occurrence of adverse effects in the various plasma level-groups, including the higher exposure groups.

All appropriate clinical tests and animal tests were done in order to address safety. The extent and duration of exposure is limited in the special populations.

Benefit-risk

The efficacy of VIRACEPT in the treatment of HIV infection has been well established in clinical trials and in the general HIV population over the past 5 years. HIV infection is becoming better controlled through the availability of a number of highly active agents, however this availability has also increased the number of tablets the patient must take daily. This pill burden can lead to individual patients becoming less compliant with the danger of a drug holiday and the possibility of increased resistance. The current dosage regimen for VIRACEPT contributes to this daily pill burden since the recommended dose is 1250 mg twice daily, a total of ten 250-mg tablets. There is clearly a high medical need for reducing the number of VIRACEPT tablets and hence the Sponsor has developed the 625-mg tablet, which reduces the daily number of tablets by 60 %. When studied in a formal bioequivalence study, however, the new formulation was found to be moderately more bioavailable. Whereas this is not known whether the increased bioavailability confers additional efficacy, there could be a risk of more adverse events as a result of the higher exposure.

Nelfinavir is considered to be a well-tolerated HIV protease inhibitor, with an adverse event profile comprising four typical adverse events, diarrhea, flatulence, nausea, and rash. The sponsor has examined the relationship between exposure to nelfinavir and frequency of these four adverse events, in particular, to discern the extent of any risk associated with the increased bioavailability of VIRACEPT 625 mg tablet. Overall, the sponsor concludes that, although certain adverse events, such as asthenia and diarrhea, did increase in frequency with exposure, the adverse event profile of the 625 mg tablet is unlikely to be markedly different to the current 250 mg regimen and the events themselves remain manageable.

The development of the 625 mg formulation of VIRACEPT markedly reduces the pill burden. Medical events will be manageable with the new 625-mg formulation, as they are now with the existing 250-mg regimen. Overall, because of likelihood of increased compliance and the lack of new or unacceptable risks with higher concentrations of nelfinavir, the new 625-mg formulation of VIRACEPT presents a favorable benefit to risk profile.

Drug-drug interactions

The drug-drug interaction studies indicate that NFV *in vivo* metabolism is mediated primarily via CYP3A4 and CYP2C19. *In vitro* data (NDA 20-779) indicate that NFV is metabolized primarily by CYP3A4 (~50 %) and CYP2C19 (~33 %) indicating that CYP3A4 and CYP2C19 inducers or inhibitors are likely to affect NFV metabolism. 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 that support the *in vivo* findings. Ritonavir (RTV) is a CYP3A4 inhibitor, whereas delavirdine (DLV) inhibits both CYP3A4 and CYP2C19. Coadministration of RTV with nelfinavir (Kurowski *et al.*) resulted in an approximately 50 % increase in NFV exposure (Table I) and coadministration of nelfinavir with delavirdine (Studies 0070, 0073 and 711) increased NFV exposure by ≥ 100 %. In the DLV-NFV study (M/3331/0073A), 400 or 600 mg DLV (three times daily) + 750 mg NFV (three times daily), DLV increased NFV exposure by 107 %. Collectively, data from these two studies indicate that DLV is a better 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.

Summary of Selected Drug-Related Adverse Events

This Reviewer considers diarrhea to be an important and drug-related adverse effects.

Additional, the issue of arrhythmogenicity is important, but it is unclear whether it is directly related to the use of the drug. The Cardio-Renal Consultants concluded that the principal proarrhythmic risk of NFV emanates from interference with the metabolic pathways of other clearly proarrhythmic drugs. They also felt that the bolded warning could be improved by specifying the risk of drug interaction, [redacted]

Review of the post marketing data while showing a prevalence of cardiac dysrhythmias in association with NFV, because of the confounding of the data, a definite causal association could not be made.

The risk of diarrhea is expected to be greater with the increased NFV exposure in the 625mg formulation. The Agency has proposed labeling changes to reflect this increased risk of diarrhea.

E. Summary of Critical Safety Findings and Limitations of Data

The Integrated Safety Summary indicates that of the adverse events typically associated with nelfinavir, only diarrhea showed a tendency to increase with increased exposure, yet the rate of diarrhea in these studies varied widely. Nelfinavir-associated diarrhea is generally a manageable reaction and rarely interrupts therapy; patients infrequently discontinued study due to diarrhea.

No unexpected adverse events appeared outside the safety profile associated with the use of nelfinavir. Trends for higher reporting of adverse events at higher exposures cannot be confidently detected in this study.

The Statistical Reviewer noted an increase frequency of "eye disorder" and "acne". This Reviewer feels that this finding may be as a result of multiple comparisons and the coding of the "eye disorder" and "acne" diagnoses.

Data limitations

1. Data Pooling

Integrated safety analyses are required to have sufficient power to detect rare events and for subgroup comparisons. Data pooling improves the precision of risk or incidence estimates, and improves the power for detecting differences between groups. However, the data from the studies were pooled by adding the number of events observed, and dividing the results by the total number of patients included in the group. Pooling ignores the validity of the comparisons, combining various trial designs, different doses of drugs, with different study design and conduct. This exposes the analysis to a particular bias called Simpson's paradox (J R Statist Soc B 1951, 2:238-241, Br Med J 1994, 309:1480-1481).

This paradox can arise if the disease states are different, such as pooling treatment naïve and treatment experienced patients, randomized, double-masked studies with open-label studies, studies conducted with different drug combinations.

Data Pooling may cause confounding of the data. In this case, the findings and the conclusions remained fairly consistent across pooled populations and individual study groups.

2. Imputed dose levels in PP2 and impact on conclusions

   Patients in study 73B were assumed to have plasma AUC NFV levels in the high range of > 61, although PK measurements were not actually recorded, and merely imputed from the results of the PK studies performed on Study 73A patients. Although the assumption is a fair one, it is possible that there were subjects in 73B who did not AUC levels in the high range.

3. Polypharmacy and confounding of QT prolongation data.

   Polypharmacy is part of the standard of care in HIV disease. Usually HIV patients are on 3 or more different anti-HIV medications. When an AE is noted, it may be impossible to definitively attribute the AE to any one drug.

4. Exposure- response analysis

   Although the co-administration of 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. Additionally, it is unclear if the high systemic NFV exposures would be expected to correlate with adverse events such as diarrhea; diarrhea is a local effect (GI) and may not be affected by DLV's inhibition of NFV metabolism that appears to occur in the liver.

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

The major potential limitations of the exposure-response analyses are:

a.) That the predictions are based on a limited number of subjects (n=28, Study 713) and

b.) 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.

c.) The accuracy of the AUC_{24} estimation is not certain, because NFV exhibits diurnal variation, where morning trough concentrations are twice as high as evening trough concentrations (BID regimen) and the analyses is based on extrapolation from non-steady state data (single dose, rather than multiple dose data). It should be further noted that the pooled exposure-response data used in the analyses might 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).

d.) Food effect and food variability

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 %). The high variability associated with the fasted condition can impact PK results particularly in long-term trials (see Exposure-Response, PK Reviewer's Note).

Integrated review of Cardiac Safety, and potential for QT Prolongation.

The safety review of the cardiac effects of NFV was performed under the following headings:

1. Examination and analysis of the pre-clinical testing on NFV.

2. Comparative analysis (by plasma level) of patients presenting with cardiac-related events.

3. Analysis of reported cases of TdP and QT prolongation and causality determination.

The following materials were examined:
1. NDA 21-503
2. Periodic Safety Review Update [PSUR] -4/2001- 3/2002
3. Post marketing adverse event reporting (Spontaneous Reporting)
4. AE Safety reports in other markets (Europe, Japan)
5. The literature
6. Patient databases and registries

Results of Post marketing surveillance provided the impetus for this more specific evaluation of cardiac safety analysis.

A. <u>Examination and analysis of the pre-clinical testing on NFV.</u>

The following animal (preclinical) experiments were performed:

1) EFFECT OF NFV and Hydroxy-t-butylamide (M8) on Dog Isolated Purkinje Fibres in vitro.

Nelfinavir (NFV) at 0.1, 0.3, 1 um concentration, and Hydroxy-t-Butylaimide (M8) at 0.1, 0.3, 1 µm concentration was administered in the Purkinje fibre preparation. D-sotalol was used as a positive control. The fibres treated with NFV and M8, were without significant effect on resting membrane potential, AP amplitude, V max, and action potential duration.

The conclusion was that NFV and M8 do not have a significant effect on the repolarization phase of cardiac action potential.

2) EFFECT OF NFV and M8 on HERG Potassium Channels, using the in vitro whole cell patch clamp technique.

The HERG or potassium channel underlies the rapidly activating delayed rectifier current. Agents that block the HERG channel prolong the action potential by delaying the repolarizing phase. After a 5-minute application of NFV at 1 and 3 u m concentration, there was a 13.4 and 35.4% decrease in current, and M8 at 10um there was a 18.8% reduction in current. Dofetilide was used as a positive control. Time matched controls gave neglible reductions in current.

The conclusion was that there was no significant effect of NFV on HERG current at clinically relevant plasma concentrations. The free plasma concentration of NFV used in these experiments was 10 times the concentration of clinically efficacious doses of NFV.

3) To examine the effect of NFV and M8 on action potentials evoked in dog isolated Purkinje fibres at stimulation frequencies of 0.3 Hz, 1 Hz and 3 Hz, using NFV at 0.3μm, 1μM and 3 μM and M8 at 1μM, 3μM and 10μM concentration.
Purkinje fibres are particularly sensitive to agents known to prolong QT intervals in animals and man.

CONCLUSION:

NFV at 3uM concentration has an effect on cardiac AP duration. M8 at 10 uM concentration caused statistically significant reductions in AP duration. It was concluded that at supratherapeutic concentrations, NFV or M8 might have an effect on cardiac channels.

It was concluded that the NFV and its metabolite M8, at supratherapeutic concentrations might have an effect on action potential duration, and cardiac channels.

Overall, the animal studies did not provide a 'signal' that NFV nor its metabolites, at physiological doses were responsible for delaying the repolarization phase of the cardiac action potential. Results of clinical studies however, are final arbiter of QT risk, and are the final determinants of human effects.

B. Comparative analysis (by plasma level) of patients presenting with cardiac-related events.

Cardiac adverse events were reported in pooled-population-1, and study 73B. The results are reported in tabular form, split by AUC.

Pooled Population 1: Treatment-emergent Cardiac Adverse Events Split by AUC

Adverse Event COSTART Term	AUC mg.h/L <41 N=142 n (%)	41-61 N=123 n (%)	>61 N=52 n (%)	Total N=317 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)

Source: NDA 21-503, Volume 15, table 10

Study 0073B Treatment-emergent Cardiac Adverse Events

Adverse event COSTART Term	DLV + NFV + d4T	DLV + NFV + ddI	DLV + NFV + d4T + ddI	NFV + d4T + ddI	Total N=173
	N=43 n (%)	N=45 n (%)	N=42 n (%)	N=43 n (%)	n (%)
Arrhythmia	0	0	0	1 (2.3)	1 (0.6)
Bradycardia	0	0	1 (2.4)	0	1 (0.6)
Syncope	1 (2.3)	0	0	0	1 (0.6)
Tachycardia	0	1 (2.2)	0	0	1 (0.6)

Source: NDA 21-503: Volume 15, table 26

Conclusions from the cardiac adverse event analysis as shown in the prior two tables were as follows:

1) No trend of cardiac events frequency was noted among the three plasma AUC- level groups.
2) Neither serious adverse events nor discontinuations in therapy were noted in association with cardiac events.
3) No trend regarding severity or increased numbers of cardiac adverse events were noted in the high exposure group.
4) The most frequent cardiac AE was tachycardia.
5) Of the 23 patients with cardiac events, 9 patients exhibited similar events prior to dose start date, and were considered as a pre-existing condition.

There was a low frequency of cardiac adverse events in all studies. Neither higher incidence nor the severity of reported events was greater in groups with a higher NFV exposure.

C). Analysis of reported cases of TdP and QT prolongation and causality determination.

In volume 6 of the Periodic Safety Update Report (PSUR) , the sponsor asserts that cumulatively " as of May 10, 2002 three cases reported TdP, three cases reported QT prolongation, and 2 cases reported TdP and QT prolongation". Therefore, as of May 2002, 5 cases of TdP and 5 cases of QT prolongation were reported from the Viracept post-marketing safety database.

NELFINAVIR and Torsade de pointes(TdP)

Torsades de pointes: All 5 reports were serious. Four of the reports were from the USA and 1 from Switzerland. 1 case was fatal, one case continued and the outcome of 3 cases was unknown.

The mean age of occurrence was 45 years (range 34-50). The latency of onset of event following Viracept exposure was 5 days -2 years. Viracept was discontinued for all patients at the time of the event onset.
Significant medical history in these history included alcohol abuse, intravenous drug abuse and opiate addiction, tobacco use, hypokalemia and hypertension.

CASE #	Age/gender	Latency of onset	Clinical Presentation	ARV's + confounding drugs	Risk factors	Outcome
1997-000864 or 1343-12776	50/M	5 days post switching to Viracept. (prev on Indinavir)	Syncope, junctional rhythm, prolonged QT, episodes TdP	AZT, 3TC x 1.5 yrs prior to event + nizatidine		Serious AE. dev Ventric tach. Treated with pacemaker. ARV and nizatidine d/c ed
1999-002997	48/ F	Months post initiating NFV	TdP	Viracept, 3TC/AZT	Hypokalemia PH /prior hypertension, QT prolong	
1343-13233	49/F	1 month post NFV. Prev on 3TC, AZT	4 episode of pre syncope prior to onset of events, TdP , QT prolong	NFV, fluconazole, omeprazole d/c ed		Temporary pacemaker
1343-13234	34/ F	NFV of unknown duration		Fluoxetene x 1 year	Low K+	
1343-13225	44/M	? mths on NFV; 3TC, AZT, atenolol	Recurrent syncope+ prol QT	Atenolol, methadone, oxazepam	iv drug abuse, alcohol, hypertension	Discovered dead in bed duiring 2nd hospitaliz.

NFV and QT prolongation

QT prolongation: Three of the 5 reports were from the USA, 1 from France, and 1 from Switzerland. The outcomes of the events were as follows: 1 was fatal, 1 recovered, 1 continued, and the outcome was unknown in 2 cases. The mean age was 44 years (37-49). The latency range of onset of the event post exposure to Viracept was 35 days-2 years.

CASE #	*Age/gender*	Latency of onset	Clinical presentation	ARV's + other confounding drugs	Outcome
1343-13233	49/F	1 month NFV. 3TC AZT longer		NFV, 3TC,AZT Fluconazole x2 yrs;Omeprazole x7mths	Defibrillation + temp pacemaker
1343-13525	44/M	? mths on NFV; 3TC, AZT, atenolol	Recurrent syncope+ prol QT	Atenolol, methadone, oxazepam	Discovered dead in bed duiring 2nd hospitaliz.
1997-000283	37/M	10 wks post NFV	Syncope, bradycardia. HR 44/min, QT 616msec	Diphenoxylate/ atropine	Pt d/c ed from study. Brady persisted prior to & during study
1999-00216	?/M	?	Bradycardia+ QT prolongation	Viracept, 3TC, d4T	?
1999-002958	44/F	11 months	Intermittent compl Ht block 11 months post ARV	Propyl thiouracil, clonazepam,isoniazid, anemia,goitre	

Source: FDA compilation of data from PSUR 4/2001-3/2002

SUMMARY OF Tdp and QT prolongation cases seen in association with NFV

The available data is summarized in tabular form below.

The data is significantly confounded by hypokalemia and other drug use, which precludes making a definitive causal association between NFV and TdP and QT prolongation.

	Torsades de pointes	**QT Prolongation**
OUTCOME	5 serious: 1 fatal, 1 continues, 3 unknown	1 fatal; 1 recovered; 1 continued; 2 unknown
Mean Age	45 years	44 years
Age range	34-45 years	37-49 years
Latency of onset	5 days – 2 years	35 days – 2 years
Country of origin	4 USA, 1 Switzerland	3 USA, 1 France, 1 Switzerland
Significant Past Medical History	1999-0297-hypertension QT Prolongation 1343-13525-IV drug use/ hypertension/alcohol/iv	1999-002618-npt provided 1343-13233-npt provided
ECG	2 pts-TdP (1997-000860; 1343-13525)	No actual ECG results (1999-002618; 1343-13233
Confounding factors	1343-13234-↓K+ 1999-002997-↓K 1343-13233- Nil confounding	1999-002618 1343-13233

Source: FDA compilation of data from PSUR 4/2001-3/2002

Overall summary of cardiac safety data:

The FDA evaluated the cardiac AE's in greater detail, because a possible signal of arhythmogenic activity associated with NFV.

Review and analysis of the preclinical (animal studies), revealed that NFV and its metabolites, had some effect on the electrophysiological parameters, when tested at supraphysiological doses. The animal studies are complementary to clinical studies, and are not meant to be the final arbiter of human risk. Though they are not absolutely predictive of human effects, they are complementary to clinical studies and measure potential risk relevant to humans.

The clinical cardiac adverse events were infrequent. Additionally, there is no trend with the occurrence of adverse cardiac event being associated with higher plasma-AUC levels.

After analyzing the reported cases of Torsade de Pointes and QT prolongation, in association with NFV, assigning causality was difficult because of the presence of other risk factors. It was difficult to attribute these effects solely and directly to NFV because of severe confounding of the study data.

VII. Dosing, Regimen, and Administration Issues

The proposed treatment regimen is Viracept 1250 mg po bid, to be administered with food.

An exposure-response relationship has been established for Viracept 625-mg. This is believed to be as effective as the 250mg-dose regimen, without much change in side effect profile. This tablet is taken with food, and is given twice daily.

Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No significant pharmacokinetic differences have been detected between males and females.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Pharmacokinetic differences due to race have not been evaluated.

The pharmacokinetics of nelfinavir has not been studied in patients over 65 years of age. Clinical studies of VIRACEPT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

C. Evaluation of Pediatric Program

Nelfinavir was studied in one open-label, uncontrolled trial in pediatric patients ranging in age from 2 to 13 years. In order to achieve plasma concentrations in pediatric patients which approximate those observed in adults, the recommended pediatric dose is 20-30

mg/kg given three times daily with a meal or light snack, not to exceed 750 mg three times a day.

A similar adverse event profile was seen during the pediatric clinical trial as in adult patients.

D. Comments on Data Available or Needed in Other Populations

The pharmacokinetics of nelfinavir have not been studied in HIV positive patients with hepatic or renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal. A multidose study of NFV in patients with hepatic impairment is ongoing.

X. Conclusions and Recommendations

An assessment of safety has been conducted because of the potential for higher nelfinavir exposure with the 625-mg tablet dosage regimen when compared with the 250-mg population. Two populations were assessed for whether adverse events increased with increasing exposure to NFV.

An analysis of PP 1 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).
These 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 PP1.
Of the adverse events typically associated with nelfinavir, only diarrhea showed a tendency to increase with exposure yet the rate of diarrhea varied between studies.

The development of the 625 mg formulation of VIRACEPT markedly reduces the pill burden. Medical events will be manageable with the new 625-mg formulation, as they are now with the existing 250-mg regimen. Overall, because of convenience and possible increased compliance, and the lack of new or unacceptable risks with higher concentrations of nelfinavir, the new 625-mg formulation of VIRACEPT presents a favorable benefit to risk profile.

A. Conclusions

Over the past 6 years, Viracept has been noted to be efficacious in treating HIV disease.

This newer 625-mg formulation offers an increased exposure, with continued efficacy and without substantial increases in adverse effect. Cardiac adverse events, particularly malignant dysrhythmias, have been reported in association with NFV, but a causal association has not been made. The frequency of nelfinavir–associated diarrhea may be increased with the 625-mg formulation, but this adverse event is felt to be very treatable.

Any safety risk(s), are far outweighed by the benefits of the drug.

Although there are other effective anti-HIV drugs in the protease inhibitor class, this formulation will offer the HIV treatment community with another efficacious treatment option. Adverse event risk is covered in the labeling changes. eg proarrhythmic risk and diarrhea.

B. Recommendations

The Sponsor's submission for Viracept (nelfinavir mesylate) 625-mg formulation is judged to be approvable. The evidence of effectiveness and safety, appear sufficient.

A.) Changes are needed in the labeling to reflect the following:

1) The principal proarrhythmic risk of nelfinavir seems to originate from interference with the metabolic pathway of other proarrhythmic drugs.

2) Care needs to be exercised in prescribing this drug in the presence of co-administered drugs known to increase the possibility of arrhythmic events, and that are metabolized by CYP 3A4.

3) The label should be updated to include the statement that NFV is metabolized by CYP2C19. The information provided by the Sponsor regarding the role of the CYP2C19 enzyme in nelfinavir metabolism is adequate to make labeling 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).

B) Ongoing Pharmacovigilance, with periodic clinical reviews and cumulative reports on the 625mg-formulation.

These labeling changes have been proposed to the Sponsor.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-503 (nelfinavir)

Sponsor: Agouron Pharmaceuticals (Pfizer)

Submission: NDA for higher dose tablets.

Review date: 19 February 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-503

HFD-530/Division Director

HFD-530/Gibbs

HFD-530/O'Neill

Background

The Division of Cardio-Renal Drug Products is asked to comment upon the arrhythmogenic potential of nelfinavir (Viracept), an approved protease inhibitor for the treatment of HIV.

Response

At 1 μM (near the limit of solubility and about 10x the mean or 2x the maximum plasma levels seen in man), nelfinavir had little or no effect on HERG currents or action potential duration (isolated dog Purkinje fibers), experiments in which sotalol was an active control.

Materials provided for review and the current label for nelfinavir do not address effects on heart rate or QT interval in controlled studies of nelfinavir.

Reported adverse events in controlled studies include syncope (<1%), but no life-threatening arrhythmia. No cardiac adverse events are mentioned in the current label for nelfinavir.

Post-marketing data include 5 cases of torsades de pointes, one fatal, on nelfinavir, and another 5 cases of increased QT, one fatal. A consultative review from ODS (5 October 2001) describes 15 cases of torsades or QT prolongation in association with 5 of 6 approved protease inhibitors. Given all the uncertainties in denominators, the incidence does not appear to be different with different protease inhibitors, although the point estimate is the highest for nelfinavir.

Nearly all the cases of torsades or QT prolongation on nelfinavir are confounded by the use of other drugs thought to prolong QT. Current labeling contains a bolded warning against use of nelfinavir, which is a CYP 3A4 inhibitor, with QT-prolonging drugs that are 3A4 substrates.

It is probably fair to conclude that a comprehensive evaluation of the arrhythmogenic potential of nelfinavir has not been done. However, it seems most likely that the principal proarrhythmic risk comes from interference with the metabolic pathways of other clearly proarrhythmic drugs. In this regard, the bolded warning could be improved by

The Division of Cardio-renal Drug Products is pleased to have the opportunity to review these data. Please feel free to contact the Division for further clarification or discussion.

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